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THE HEART IN RHEUMATOID ARTHRITIS

A STUDY OF THIRTY-EIGHT AUTOPSY CASES

DENNISON YOUNG, M.D.,* AND JOHN B. SCHWEDEL, M.D.†
NEW YORK, N. Y.

ALTHOUGH a common etiological background for chronic rheumatoid arthritis and rheumatic heart disease has been accepted in Europe, principally by German authors,[1-4] but also by some of the English,[5-10] French,[11-16] and Scandinavian writers,[17] this concept has by no means been established in this country. The prevailing opinion here has been that, when chronic structural joint changes and evidence of rheumatic carditis co-exist, it is a rather rare combination of two distinct clinical entities. The belief is that either they are present concurrently,[18, 19] or that the arthritis was preceded by acute or subacute rheumatic fever.[20, 21] The most recent *Primer on Arthritis,*[22] published by the American Rheumatism Association, holds this view.

Unfortunately, this concept of an etiological difference persists because of the lack of post-mortem studies of a sufficiently large number of patients with rheumatoid arthritis, for, as pointed out forty years ago by Pribram,[2] and later by Klinge,[4] the clinical diagnosis of heart disease in patients with arthritis is infrequently made. Baggenstoss and Rosenberg,[23] in reporting a series of twenty-five cases in which there were autopsies, found twenty cardiac lesions, fourteen of which were assumed to be rheumatic. The clinical diagnosis was made in only seven of these cases. In Bayles'[24] recent paper, of the six cases in which rheumatic heart disease was found at necropsy, the clinical diagnosis had been made in four.

It is the purpose of this report to present the post-mortem and related clinical data in thirty-eight cases of rheumatoid arthritis in adults. In

The opinion and views set forth in this article are those of the authors, and are not to be construed as reflecting those of the United States Army or of the Navy Department.

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From the Medical Service, Montefiore Hospital, New York, N. Y.
*Captain, Medical Corps, Army of the United States.
†Lt. Comdr., Medical Corps, United States Naval Reserve.

TABLE I

CLINICAL AND NECROPSY DATA IN THIRTY-THREE CASES OF RHEUMATOID ARTHRITIS AND HEART DISEASE

CASE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE HEART DISEASE DISCOVERED (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT			HEART INVOLVEMENT		CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
					TYPE OF ONSET	COURSE	DEFORMITY	CLINICAL	POST MORTEM			
1	M	18	36	63	Pain in right hip	Progressive, multiple deformity. Bedridden 25 years	Upper and lower extremities, spine	Enlarged heart M.S., M.I., A.I. B.P. 130/50	Weight 560 Gm. Healed rheumatic endocarditis of aortic valve. Calcification of aortic leaflets. Left auricular endocarditis	Congestive failure Bronchopneumonia	Left knee joint-cavity obliterated by fibrous ankylosis	Bilateral iritis
2	F	28	38	47	Acute phalangeal arthritis	Frequent episodes of polyarthritis. Bedridden 13 years	Upper and lower extremities, spine	Enlarged heart A.I., A.S. B.P. 170/94	Weight 330 Gm. Healed rheumatic endocarditis of mitral valve. Indeterminate endocarditis of mitral valve	Uremia Congestive failure Bronchopneumonia	Acute diffuse glomerulonephritis	
3	M	?	–	53	Rigidity of neck	Insidious, progressive multiple deformity	Fingers, wrists, elbows, shoulders, knees, spine	Heart sounds poor and distant. B.P. 110/70	Weight 220 Gm. Adhesive pericarditis. Aortic valve slightly thickened	Bronchopneumonia	Amyloidosis of liver and spleen	
4	F	23	–	48	Painful swelling of toe in 2nd month of pregnancy	Post-partum multiple involvement. Recurrence with progressive deformity	Spine, upper and lower extremities except hips and shoulders	"No evidence of organic heart disease" B.P. 110/70 ECG—L.A.D.	Obliterative pericarditis	Bronchopneumonia		

5	M	20	38	49	Acute polyarthritis	Progressive pain and rigidity of spine. Insidious deformity	Spine (marked), hips, knees, shoulders	Enlarged heart A.I. B.P. 130/10 ECG—L.A.D. T_1, T_2 inverted, P.R. 0.25	Weight 850 Gm. Healed rheumatic endocarditis of aortic valve	Congestive failure	Acute nephritis Calcification of spinal ligaments	
6	F	35	–	48	Pain in ankles	Multiple, insidious deformity. Acute episode at 46 years of age	Upper and lower extremities	Heart sounds distant B.P. 88/50	Weight 300 Gm. Obliterative pericarditis	Bronchopneumonia		
7	M	29		32	Painless swelling right knee	Insidious, progressive, multiple deformity	Spine (marked), upper and lower extremities		Weight 330 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Indeterminate endocarditis of mitral and aortic valves	Pulmonary infarct Bronchopneumonia	Amyloidosis of liver, spleen, and adrenals	Emaciation Premature senility
8	M	44	52	52	"Swollen hands"	Progressive insidious, multiple deformity	Upper and lower extremities	Enlarged heart M.I., A.I. B.P. 125/50	Weight 400 Gm. Healed rheumatic endocarditis of mitral valve. Slight thickening base of aortic valve	Pulmonary edema Carcinoma	Carcinoma of kidney with metastases	
9	F	32	39	39	Acute polyarthritis	Acute exacerbations with progressive deformity	Fingers, shoulders, elbows, knees, ankles	Feeble heart sounds, tachycardia B.P. 120/80	Weight 250 Gm. Acute rheumatic pericarditis	Rheumatic fever Congestive failure		Rheumatic fever
10	F	52	56	66	Acute polyarthritis	Progressive deformity. Bedridden 9 years	Spine (marked), upper and lower extremities	Enlarged heart M.I.	Weight 220 Gm. Chronic adhesive pericarditis. Healed rheumatic endocarditis of mitral, aortic and tricuspid valves. Left and right auricular endocarditis	Pulmonary tuberculosis	Amyloidosis of liver and kidneys Left knee joint-fibrous obliteration of cavity; bone atrophy	

TABLE I—CONT'D

CASE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE HEART DISEASE DISCOVERED (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT			HEART INVOLVEMENT		CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
					TYPE OF ONSET	COURSE	DEFORMITY	CLINICAL	POST MORTEM			
11	M	44	8	48	Acute rheumatic fever with joint and cardiac involvement	Recurrent rheumatic fever at 9, 10, and 11 years. Insidious, progressive deformity at 44 years of age	Hands, fingers, feet	Enlarged heart M.I., M.S., A.I., A.S. B.P. 168/68 ECG—L.A.D. auricular fibrillation and flutter	Weight 500 Gm. Focal adhesive pericarditis. Healed rheumatic endocarditis of mitral, aortic and tricuspid valves. Active endocarditis of mitral and aortic valves. Left and right auricular endocarditis. Calcification aortic leaflets	Cerebral embolus Bronchopneumonia Congestive failure	Amyloidosis of liver, spleen, kidneys, and adrenals	
12	F	47	53	60	Pain in left shoulder	Insidious, progressive, multiple deformity	Upper and lower extremities, spine	Enlarged heart A.I., M.I. B.P. 165/60; 170/100 ECG—L.A.D. high voltage, intraventricular block	Weight 400 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Calcification base of aortic valve	Bronchopneumonia Congestive failure	Infarcts of spleen and kidneys	Hypertension Subcutaneous nodules
13	F	13		21	Acute arthritis left wrist with residual deformity	Acute episodes with deformity and ankylosis. Bedridden 4 years	Spine (marked), fingers, wrists, shoulders, knees, ankles	"Heart normal"	Weight 250 Gm. Adhesive pericarditis. Healed rheumatic endocarditis of mitral valve. Left auricular endocarditis. Petechial epicardial and subendocardial hemorrhages	Bronchopneumonia Congestive failure	Pyelonephritis Renal calculi Terminal skin and visceral hemorrhages	

14	M	49		50	Acute polyarthritis with residual deformity	Progressive multiple deformity	Wrists, fingers, elbows, knees, spine	Sounds weak "tic-tac" quality Apical systolic murmur B.P. 120/70 ECG—low voltage QRS, high in Leads II and III	Weight 430 Gm. Adhesive pericarditis. Arteriosclerotic thickening of mitral, aortic and tricuspid valves	Lobar pneumonia	Diffuse nephritis	Subcutaneous nodules
15	F	58	61	65	Pain in right shoulder	Insidious, progressive, multiple deformity	Upper and lower extremities, spine	Enlarged heart Sounds fair Harsh apical systolic murmur. B.P. 190/80; 150/74 ECG—L.A.D.	Weight 500 Gm. Adhesive pericarditis	Congestive failure		Hypertension
16	F	12	11½	27	Acute rheumatic fever (joint involvement) at 11 years of age	Recurrence with cardiac involvement at 11½ years of age with residual joint deformity. Recurrence at 20 and 27 years of age	Fingers, spine	Enlarged heart M.I., M.S., A.S., A.I. (Predominant) B.P. 190/0 ECG—R.A.D. high voltage P.R. 0.42 sec., intraventricular block	Weight 820 Gm. Focal adhesive pericarditis. Healed rheumatic endocarditis of mitral and aortic valves. Left auricular endocarditis. Aschoff bodies in myocardium	Sudden death		Active rheumatic fever with congestive failure
17	F	17	50	51	Pain and swelling of toes	Progressive, insidious, multiple deformity. Bedridden 16 years	Spine, upper and lower extremities	Enlarged heart Persistent tachycardia Paroxysmal auricular fibrillation B.P. 104/54	Weight 270 Gm. Obliterative pericarditis. Acute interstitial myocarditis	Congestive failure Jaundice Coma	Biliary cirrhosis Adenoma of thyroid	Episcleritis
18	M	46	53	54	"Rheumatism"	Recurrence 3 years later with further deformity—progressive	Upper and lower extremities	Enlarged heart A.I. B.P. 125/45 ECG—R.A.D.	Weight 450 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Left auricular endocarditis	Bronchopneumonia Congestive failure		

TABLE I—CONT'D

CASE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE HEART DISEASE DISCOVERED (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT			HEART INVOLVEMENT		CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
					TYPE OF ONSET	COURSE	DEFORMITY	CLINICAL	POST MORTEM			
19	M	50	50	56	"Rheumatism" at 12 years of age	Multiple joint pains with progressive deformity	Spine, upper and lower extremities	Enlarged heart M.S., M.I., A.I. B.P. 115/68 ECG—L.A.D., auricular fibrillation	Weight 490 Gm. Recurrent active endocarditis of mitral and aortic valves. Fibrinous pericarditis. Left auricular endocarditis	Congestive failure Lipoid pneumonia		
20	M	19	19	31	Pain in spine with progressive stiffness an convexity	Periodic exacerbations for 4 years with pain in other joints	Spine (predominantly Marie-Strümpell), shoulders, elbows, wrists, fingers, hips, knees	Enlarged heart M.S., M.I., A.S., A.I. B.P. 110/30 ECG—L.A.D. QRS widened paroxysmal auricular fibrillation	Weight 530 Gm. Healed rheumatic endocarditis of mitral, aortic, tricuspid and pulmonic valves. Bacterial vegetative endocarditis mitral valve. Left and right auricular endocarditis. Focal adhesive pericarditis. Scarred Aschoff bodies in myocardium	Pulmonary infarction Congestive failure	Splenic infarcts	
21	M	31	33	41	"Rheumatism" at 14 and 17 years of age	Acute polyarthritis at 31 years of age with progressive deformity	Spine, wrists, hands, knees, hips	Enlarged heart M.I., M.S. Pericarditis B.P. 110/64 ECG—R.A.D. Premature ventricular beats	Healed rheumatic mitral endocarditis. Obliterative pericarditis	Bronchopneumonia Congestive failure		Polyglandular syndrome

22	F	59		64	Multiple joint pains	Progressive deformity. Bedridden 3 years	Spine (marked), upper and lower extremities	No cardiac enlargement M.I.	Weight 150 Gm. Fibrinous pericarditis. Brown atrophy of heart. Calcification base of mitral, aortic, and tricuspid valves	Bronchopneumonia Congestive failure		
23	F	31		40	Pain in left knee with deformity	Two years later progressive, multiple deformity	Hands, wrists, knees, hips, ankles, spine	"No heart disease"	Weight 230 Gm. Healed rheumatic mitral endocarditis. Pedunculated, hyalinized nodule mitral valve	Bronchopneumonia Congestive failure		
24	M	27	36	40	Stiffness in back. Acute arthritis at 35 years of age	Progressive multiple deformity	Spine (marked), upper and lower extremities	Enlarged heart A.I. B.P. 130/60	Weight 800 Gm. Healed rheumatic endocarditis of aortic valve. Healed Aschoff bodies in myocardium	Congestive failure Bronchopneumonia		
25	F			75		Progressive deformity	Wrists, hands, elbows, hips, knees	No cardiac diagnosis B.P. 140/70 ECG—L.A.D.	Weight 300 Gm. Acute fibrinous pericarditis	Pericarditis Congestive failure Bronchopneumonia		
26	F	57	72	73	Pain and deformity, knees	Progressive, insidious, multiple deformity	Spine (marked), upper and lower extremities	Enlarged heart A.S., M.I.	Weight 300 Gm. Healed rheumatic mitral and aortic endocarditis. Left auricular endocarditis	Uremia	Partial necropsy (heart only)	
27	M	50	70	70	Acute polyarthritis	Frequent recurrences with progressive deformity	Wrists, fingers, knees	Enlarged heart Syphilitic aortitis B.P. 105/58	Weight 500 Gm. Healed rheumatic mitral, aortic, and tricuspid endocarditis. Adherent pericardium. Syphilitic aortitis	Congestive failure	Cirrhosis of liver	Wassermann 4+

TABLE I—CONT'D

CASE	SEX	AGE OF ONSET OF JOINT DEFORMITY (YR.)	AGE HEART DISEASE DISCOVERED (YR.)	AGE AT DEATH (YR.)	JOINT INVOLVEMENT			HEART INVOLVEMENT		CAUSE OF DEATH	OTHER PATHOLOGIC FINDINGS	MISCELLANEOUS
					TYPE OF ONSET	COURSE	DEFORMITY	CLINICAL	POST MORTEM			
28	F	47		64	Acute polyarthritis	Frequent recurrences with progressive deformity	Wrists, fingers, shoulders, ankles, knees	Enlarged heart B.P. 230/104 ECG—marked L.A.D. Hypertensive heart disease	Weight 370 Gm. Healed rheumatic mitral, aortic, and tricuspid endocarditis with calcification at bases	Pulmonary infarct		Hypertension at 53 years of age Acute arthritis on admission
29	F	23	26	28	Stiffness of knees, hands, hips	Progressive deformity	Spine (marked), upper and lower extremities	Enlarged heart M.I.	Weight 320 Gm. Active rheumatic mitral endocarditis. Left auricular endocarditis. Adhesive pericarditis. Pericardial effusion (400 c.c.)	Streptococcal meningitis Pituitary abscess Bronchopneumonia Congestive failure		
30	F	59	63	64	"Rheumatism" of arms. Backache	Progressive, insidious deformity	Elbows, shoulders, hips, knees	Enlarged heart M.I., A.S. B.P. 130/68	Weight 230 Gm. Healed rheumatic mitral and aortic endocarditis. Calcification base of aortic valve. Left auricular endocarditis	Retroperitoneal sarcoma	Thrombosis of inferior vena cava Amyloidosis of liver	Hypertension at 60 years of age

31	F	43		60	Acute polyarthritis	Progressive, insidious, multiple deformity	Spine (marked), shoulders, wrists, fingers, knees, ankles	? enlarged heart B.P. 138/64; 180/108 ECG—L.A.D.	Weight 260 Gm. Healed rheumatic endocarditis of mitral, aortic and tricuspid valves. Calcification mitral ring; aortic leaflets. Indeterminate vegetations aortic valve	Congestive failure	Right knee joint-cavity distended with thick yellow gelatinous fluid, marked thickening of synovium; new bone formation	
32	F	54	55	60	Multiple joint pains	Progressive deformity	Upper and lower extremities	Enlarged heart A.S. (?) B.P. 180/100 ECG—L.A.D.	Weight 700 Gm. Healed rheumatic endocarditis of mitral and aortic valves. Calcification base of aortic valve. Indeterminate endocarditis aortic valve	Bronchopneumonia Congestive failure		
33	M	30		53	Pain in the neck	Episodes of acute polyarthritis	Upper and lower extremities, cervical spine	No clinical evidence of heart disease B.P. 108/78 ECG—normal	Weight 420 Gm. Healed rheumatic endocarditis of aortic and mitral valves. Fibrinous pericarditis	Bronchopneumonia Congestive failure		Subcutaneous nodles

Key to abbreviations used in table:
M.I. = Mitral insufficiency.
M.S. = Mitral stenosis.
A.I. = Aortic insufficiency.
A.S. = Aortic stenosis.
L.A.D. = Left axis deviation.
R.A.D. = Right axis deviation.

thirty-three of these cases there were cardiac lesions which were not the result of hypertension or coronary artery disease.

Although doubt has been cast on the accuracy of the separation into rheumatoid (atrophic, chronic infectious, proliferative) and osteoarthritis (hypertrophic, senile, degenerative), the cases presented in this study were chosen in accordance with the classification of "rheumatoid arthritis" based on clinical, laboratory, and radiographic observations as defined by the American Rheumatism Association.[22] Doubtful cases of isolated hip, knee, or shoulder involvement, hypertrophic changes in the spine, and those with Heberden's nodes were eliminated, as were those with a specific cause, such as tuberculosis, syphilis, gonorrhea, pyogenic infection, gout, and central nervous system disease. All patients included in this material suffered from an inflammatory polyarticular process which was progressive in character and resulted in deformity and disability. These patients were closely followed in the hospital and in the pavilion for the disabled for months to years (twenty-six years in Case 1) before death occurred. The roentgenograms were characteristic of this disease in the earlier stages, but with advancing years, additional hypertrophic degenerative changes were noted. In many cases there was anatomic verification of the nature of the joint disease.

Gross and histologic study was made in all cases. Cardiac lesions designated as rheumatic were usually apparent from the gross appearance alone. The criteria employed were thickening of the edges of the mitral and tricuspid leaflets, plus thickening and shortening of their chordae tendineae, thickening and rolling of the free edges of the aortic leaflets, frequently with commissural adhesions, and thickening and occasionally calcification of the auricular endocardium (MacCallum lesions). Young Aschoff bodies were found in one case only. The microscopic appearance was characteristic. The diagnosis of acute rheumatic pericarditis was made when there was the typical "bread and butter" exudate grossly, and, microscopically, when palisading of fibroblasts and occasional round cells were seen. The lesions designated as nonspecific failed to show either sufficiently or clearly the characteristic rheumatic stigmata.

RESULTS

A detailed analysis of the results of this study is presented in Tables I and II. There were thirty-eight cases of chronic rheumatoid arthritis in adults in which necropsy was performed. Of this number, thirty-three presented cardiac lesions which were not the result of arteriosclerosis or hypertension. Of this group, twenty-four had rheumatic valvular disease, ten with pericarditis and fourteen without. The localization of valvular involvement is shown in Table III. Healed rheumatic valvulitis was present in twenty-three cases, recurrent rheumatic endocarditis of the mitral and aortic valves in two cases, and early active

TABLE II

CLINICAL AND NECROPSY DATA ON FIVE CASES OF RHEUMATOID ARTHRITIS WITHOUT RHEUMATIC HEART DISEASE

CASE	SEX	AGE AT ONSET OF JOINT DEFORMITY (YR.)	AGE AT DEATH (YR.)	TYPE OF ONSET	COURSE	DEFORMITY	POST MORTEM
1	F	35	54	Pain in toes	Acute exacerbations with progressive deformity	Upper and lower extremities, spine	Hypertensive heart disease. Arteriosclerosis of aorta and coronary arteries. Pulmonary edema
2	F	41	50	Pain in toes	Insidious, progressive	Upper and lower extremities	Old and recent coronary occlusion with posterior myocardial infarction
3	F	50	57		Insidious, progressive; bedridden past six years	Upper and lower extremities	Perivascular sarcoma of cerebrum
4	M	35	44	Pain in neck and lower back	Insidious, progressive	Marie-Strümpell spine; knees, shoulders, ankles	Intussusception of jejunum into stomach with hemorrhagic infarction and early gangrene of jejunum
5	M	57	66	Pain in arms	Insidious, progressive	Shoulders, knees, hands; marked periarthritis	Postoperative hemorrhage from a branch of the gastroduodenal artery. Old multiple coronary occlusions

TABLE III

ANATOMIC LOCALIZATION OF RHEUMATIC VALVULITIS IN TWENTY-FOUR CASES

	MITRAL	AORTIC	MITRAL AND AORTIC	MITRAL, AORTIC, AND TRICUSPID	MITRAL, AORTIC, TRICUSPID, AND PULMONIC	TOTAL
Cases without pericarditis	3	3	6	2	0	14
Cases with pericarditis	3	0	3	3	1	10
Total	6	3	9	5	1	24

rheumatic mitral valvulitis in one case. Superimposed, indeterminate, vegetative or terminal endocarditis was found in four cases, and superimposed nodular calcification of the leaflets or bases of the valves was noted in seven. Of these, except for one patient who was 48 years of age, all were 60 years or more at the time of death. A superimposed bacterial endocarditis was present in one case. This was not suspected clinically, but, on section, numerous clumps of cocci were demonstrated on the mitral valve. In one case syphilitic aortitis was also present.

There were nine cases of pericarditis without associated valvular lesions. In this group there were one case of acute rheumatic pericarditis, two of acute fibrinous but nonspecific pericarditis, and six of adherent or obliterative pericarditis. Of the ten cases of combined valvulitis and pericarditis, acute rheumatic pericarditis was present in three. In the remaining seven cases there were areas of focal adhesive pericarditis or "milk spots." Pericardial effusion (400 c.c.) was present in only one case, and was apparently due to congestive failure.

In the cases of rheumatic valvular disease, the heart weights ranged from 220 to 820 grams; the mean weight was 400 grams, which is greater than the accepted normal. Aschoff bodies in the myocardium were noted in only one case; here they were the only evidence of an active rheumatic process. Myocardial lesions which were regarded as healed Aschoff bodies were found in two cases. In many cases there were small areas of perivascular scarring, but the specificity of the lesion could not be demonstrated. Acute interstitial myocarditis was present in one case.

CLINICAL CONSIDERATIONS

There were 14 male and 19 female patients in this series. Congestive heart failure occurred in 22 cases, and was either the cause of death or preceded a terminal bronchopneumonia in these cases. As can be seen in Table IV, the majority lived beyond the usual life expectancy of patients with rheumatic heart disease. This is undoubtedly a result of the inactivity imposed upon such patients by the chronic arthritis; most of them had been completely bedridden for many years. Since the period of hospitalization was extremely long for all patients, each was examined frequently by many observers. Despite this, the clinical diag-

TABLE IV

AGE AT DEATH IN THIRTY-THREE CASES

AGE IN YEARS	20 TO 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45	46 TO 50	51 TO 55	56 TO 60	61 TO 65	66 TO 70	71 TO 75
Number of cases	1	2	2	3	1	6	5	4	5	2	2

TABLE V

CASES WITH VALVULAR DISEASE IN WHICH THE CLINICAL DIAGNOSIS WAS NOT MADE

CASE NO.	ANATOMIC DIAGNOSIS	CLINICAL DIAGNOSIS
13	Mitral insufficiency	"Heart normal"
23	Mitral stenosis and insufficiency	"No heart disease"
27	Mitral, aortic, and tricuspid insufficiency. Syphilitic aortitis	Syphilitic aortitis
28	Mitral, aortic, and tricuspid insufficiency	Hypertensive heart disease
31	Mitral and tricuspid insufficiency. Aortic stenosis	? Enlarged heart
33	Mitral and aortic insufficiency	"No heart disease"

posis of rheumatic heart disease was not made in 14 of the 32 cases (in one case there was no note concerning the heart). Of these 14 cases, the presence of obliterative or adhesive pericarditis was not suspected in 6; acute fibrinous pericarditis was not suspected in 2. The diagnosis of rheumatic valvular disease was not made in 6 cases. The anatomic lesions are shown in Table V. In the case of syphilis, apparently the

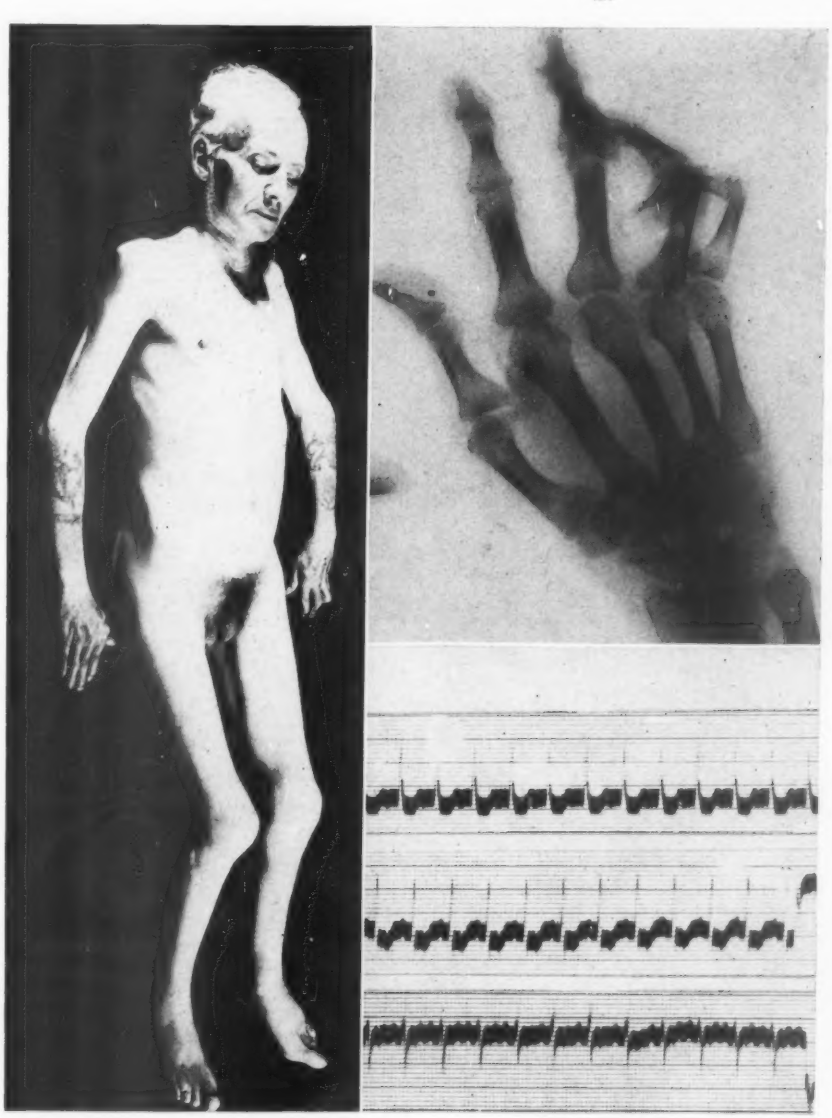


Fig. 1.—Case 11 (C. B.). *A*, Marked arthritis deformans. Premature senility. *B*, Typical advanced deformity of hand, with characteristic atrophic radiographic changes. *C*, Electrocardiogram shows 2:1 auricular flutter and left axis deviation.

signs of aortitis overshadowed the murmurs of rheumatic valvular disease. Frequently a complete, anatomic, valvular diagnosis was not made clinically, but in all such cases the presence of rheumatic heart disease was clearly recognized.

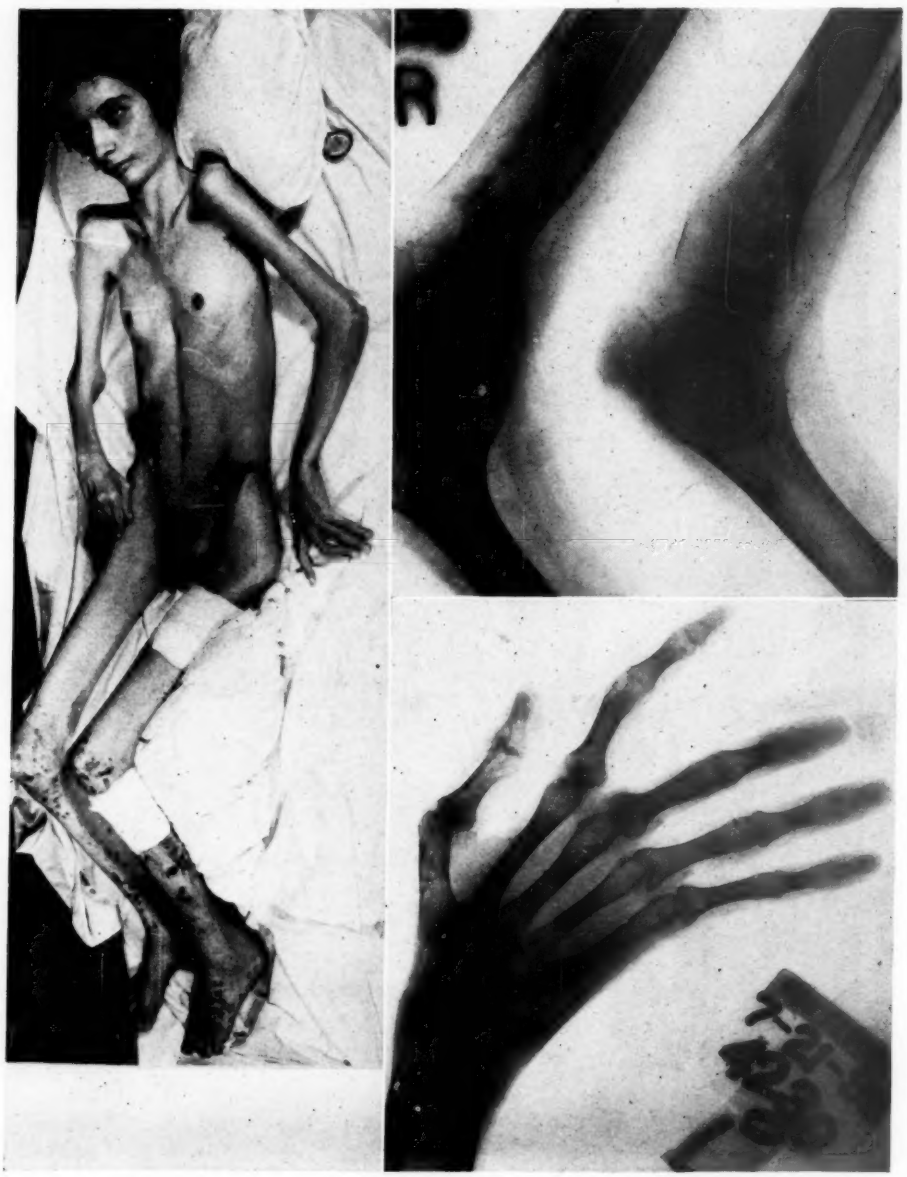


Fig. 2.—Case 13 (M. V.). *A*, Deforming, anklyosing arthritis, cachexia and cutaneous hemorrhages. *B* and *C*, Marked decalcification of bones, with narrowing of the joint clefts and broadening of the bases of the proximal phalanges.

In view of the opinion of many that patients with rheumatoid arthritis who exhibit evidence of cardiac involvement have, or have had, rheumatic fever, the clinical course of each of the thirty-three patients was closely studied. Only three (Cases 11, 16, and 20) gave a history of frank rheumatic fever earlier in life. One had an attack of joint and cardiac involvement at the age of 8 years, with frequent recurrences

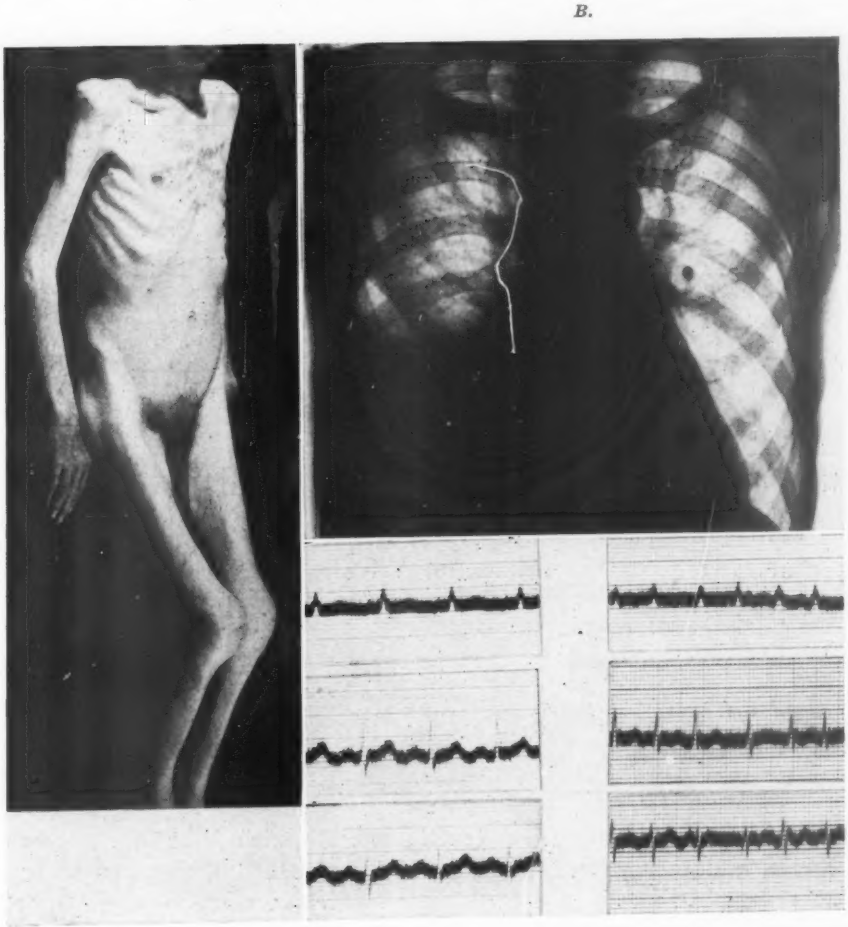


Fig. 3.—Case 19 (A. B.). *A*, Marked arthritis deformans; cachexia. *B*, Left ventricular enlargement, with straightening of upper left cardiac contour; right hydrothorax. *C*, (1) Electrocardiogram Aug. 15, 1934, shows regular sinus rhythm with broadened, notched P waves, (2) Aug. 23, 1934, auricular fibrillation present.

in childhood, but did not develop multiple joint deformities with an insidious, progressive course until the age of 44 years. The second patient had an initial attack of rheumatic fever in childhood; a recurrence six months later was followed by residual deformity. The third patient suffered from chronic active rheumatic fever for four years,

during the course of which the joints became deformed. Two patients (Cases 19 and 21) probably had rheumatic fever in childhood, although whether they had cardiac involvement at that time could not be ascertained from the history. One developed insidious, progressive deformities at the age of 50 years, the other, progressive deformity after an acute polyarthritis at the age of 31 years.

Of the remaining twenty-eight cases, in fourteen the joint deformities occurred insidiously and were progressive, and there were no attacks of acute polyarthritis. This is the so-called "primary chronic polyarthritis" of the German authors.[1, 2, 4] In an equal number, there was an attack of acute polyarthritis at the onset of the illness, followed by progressive deformity, or frequent exacerbations of acute arthritis occurred during the course of the disease ("secondary chronic polyarthritis"). The cardiac involvement in both groups was comparable in both type and extent of endocardial and pericardial involvement (Table VI). Of the five cases without cardiac involvement (Table II), the course was insidious and progressive in four. Of great interest in regard to the etiological relationship between joint and cardiac involvement is Case 9; this patient, with marked joint deformity for seven years, after repeated attacks of acute polyarthritis, was admitted to the hospital because of acute rheumatic fever. Necropsy revealed acute rheumatic pericarditis with no evidence of previous cardiac involvement.

TABLE VI

COMPARISON OF CARDIAC INVOLVEMENT IN CASES OF INSIDIOUS PROGRESSIVE DEFORMITY AND CASES WITH ACUTE ATTACKS OF POLYARTHRITIS

CARDIAC INVOLVEMENT	INSIDIOUS PROGRESSIVE ("PRIMARY CHRONIC POLYARTHRITIS")	ACUTE POLYARTHRITIS ("SECONDARY CHRONIC POLYARTHRITIS")
Pericarditis	5	4
Valvulitis	8	6
Valvulitis and pericarditis	1	4
Total	14	14

The temporal relation between the age at which joint deformity occurred and the age at which heart disease was first discovered could be reasonably ascertained in 18 cases. Fifteen cases were eliminated either because the cardiac involvement was not recognized clinically or the history was inadequate. Of the remaining cases, in 14 joint deformity occurred from one to eighteen years (average, eight years) before the discovery of heart disease. In 2 cases cardiac involvement preceded the rheumatoid arthritis. Cardiac and joint involvements were discovered concomitantly in 2 cases.

Although it would appear from this that, in the majority of instances, cardiac involvement followed a prolonged period or repeated attacks of joint involvement, this cannot be stated with assurance, for the adequacy of the initial cardiac examination is questionable. Baggenstoss

and Rosenberg[23] have expressed the opinion that the initial, although mild and slowly progressive, course of joint involvement may cause minimal cardiac damage which is not great enough to be recognized clinically. It must be remembered, however, that the arthritic constantly seeks medical care, and that each of these patients had been examined by

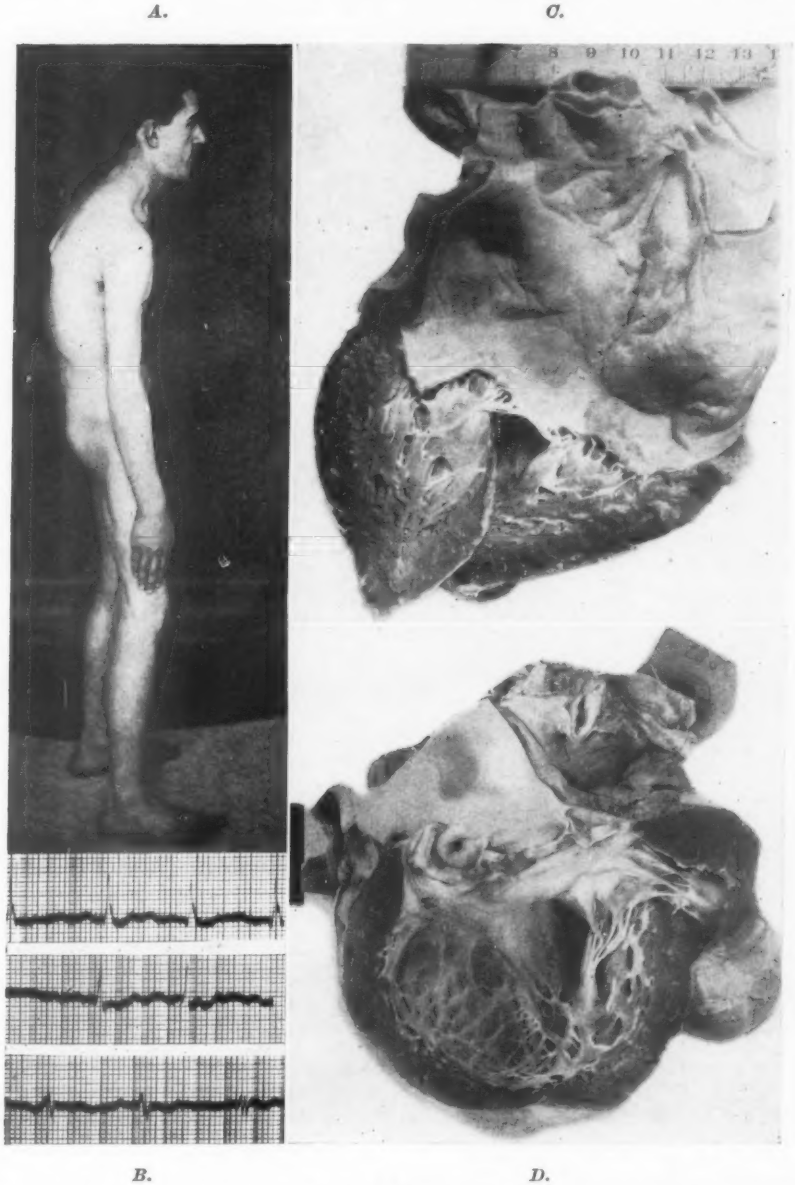
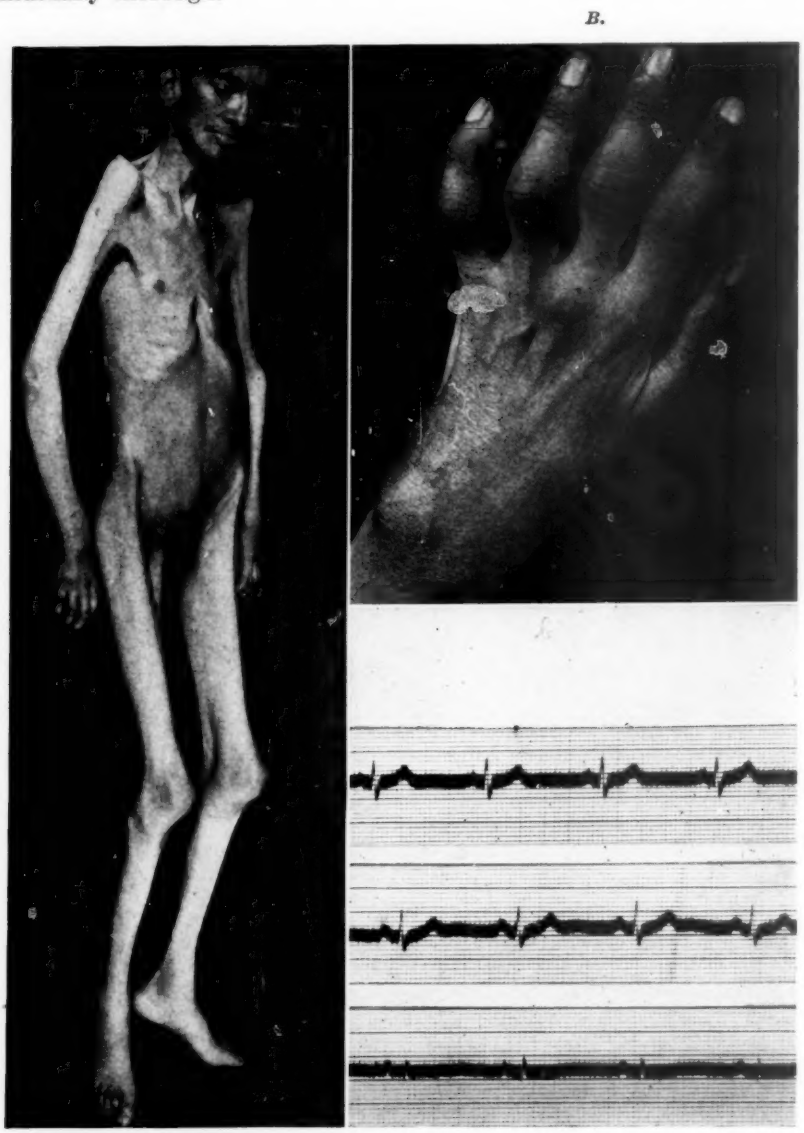


Fig. 4.—Case 20 (H. H.). *A*, Typical Marie-Strümpell spine. Arthritis of hands is also noted. *B*, The electrocardiogram shows auricular fibrillation and left axis deviation. *C*, Mitral stenosis and insufficiency. Dilatation of left auricle. *D*, Rheumatic endocarditis of aortic valve. Hypertrophy of left ventricle.

competent physicians in many clinics and hospitals, and that their records, particularly those of the Montefiore Hospital admissions, were unusually thorough.



B.

A. *C.*

Fig. 5.—Case 21 (H. G.). *A*, Marked arthritis deformans. Infantile gigantism. B, Typical fusiform swelling of proximal interphalangeal joints in rheumatoid arthritis. *C*, Electrocardiogram shows regular sinus rhythm with tendency to right axis deviation.

DISCUSSION

The paucity of adequate, complete clinicopathologic studies in the American literature has led to arbitrary separation of rheumatoid

arthritis as an entity separate and distinct from rheumatic fever and rheumatic heart disease, despite the histologic similarity of the joint changes and the identity of the subcutaneous nodules (until Collins'[25] and Bennett, Zeller, and Bauer's[26] recent papers). From the earlier studies it is not difficult to understand why such concepts came into being, for the conclusions were always based on the clinical recognition of cardiac involvement in cases of chronic arthritis. The inaccuracy of clinical recognition has already been mentioned.

Thus, McCrae,[27] among five hundred cases, found pericarditis in six and definite valvular disease in forty (8 per cent), in one quarter of which the cause may have been arteriosclerosis. Of eighty cases of arthritis deformans reported by Boas and Rifkin,[28] in fourteen (17.5 per cent) there was valvular disease clinically. Wetherby[29] reported seven cases of rheumatic heart disease (2 per cent) out of 350 cases of chronic arthritis. Monroe[30] reports an incidence of 4 per cent. Master and Jaffe,[31] judging from normal electrocardiographic observations, concluded that rheumatoid arthritis is not associated with heart disease. Dawson and Tyson[32] found a 7 per cent clinical incidence, and Bayles and McGinn[33] reported 5 per cent in one hundred consecutive rheumatoid arthritic patients. Pemberton[34] admits that there may be more in common between acute rheumatic fever and chronic arthritis than has hitherto been accepted, but concludes that they are distinct clinical entities with similar manifestations. In European countries such studies have been more frequent, and there the reported incidence ranges from Coates'[10] report of 4 per cent to Kahlmeter's[17] 40 per cent.

Probably the first description of a case of deforming arthritis with associated cardiac lesions was given by Todd,[35] in 1843. Three years later Romberg[36] described a similar case. However, it was not until 1881 that Charcot,[13] as the result of pathologic observations on a larger series of such cases, concluded that "these are not two fundamentally distinct diseases, but two manifestations of one and the same diathetic state." The results of other pathologic studies since that time indicate a rather more than fortuitous association (Table VII). In Baggenstoss and Rosenberg's[23] series the incidence of rheumatic heart disease was 56 per cent. Clawson[37] and his associates have found some form of rheumatic heart disease in 33 per cent of all cases of rheumatoid arthritis, and Bayles,[24] in 22 per cent.

In our study, 25 of 38 patients showed definite rheumatic heart disease at necropsy (65.7 per cent), and 8 others showed cardiac involvement of a nonspecific infectious nature. This percentage is rather high and, because the number of cases is not large, undoubtedly does not represent an accurate estimate of the true incidence. Nevertheless, the addition of our data to those in the literature affords a reasonable basis for concluding that an extremely close relationship exists between rheumatic fever and rheumatoid arthritis.

TABLE VII

POST-MORTEM STUDIES OF THE HEART IN CHRONIC ARTHRITIS

AUTHOR	YEAR	TYPE OF ARTHRITIS	NUMBER OF CASES				
			ARTHRITIS	ENDOCARDITIS	PERICARDITIS	PERICARDITIS AND ENDOCARDITIS	TOTAL WITH CARDIAC INVOLVEMENT
Charcot	1881	"Chronic rheumatism"	9		4		4
Kast	1901	"Primary chronic arthritis"	13	2	2		4
		"Secondary chronic arthritis"	4	2		1	3
Pribram	1902	"Primary chronic arthritis"	9		2		2
		"Secondary chronic arthritis"	4	2		1	3
Grzimek	1932	"Genuine arthritis deformans"	91	39			39
Klinge	1933	Chronic polyarthritis	10	6	1	1	8
		"Rheumatismus nodosus" of spine	1	1			1
Baggenstoss and Rosenberg	1941	Chronic infectious (rheumatoid) arthritis	25	8	4	4	16
Bayles	1942	Rheumatoid arthritis	23	4	0	2	6
Young and Schwedel	1943	Chronic rheumatoid arthritis	38	14	9	10	33

Our observations in regard to the severity of the cardiac lesions in rheumatoid arthritis are not in agreement with those of Baggenstoss and Rosenberg,[23] who found that cardiac lesions were more widespread in the hearts of patients with rheumatic fever than in the hearts of those with rheumatoid arthritis. Quantitatively, as well as qualitatively, there was no essential difference between the severity or extent of the cardiac lesions in rheumatoid arthritis and those associated with rheumatic fever. We cannot agree, either with these same authors when, because they found histologic evidence of rheumatic activity in 10 of the 14 cases, they concluded that, if a rheumatic lesion is clinically apparent, the chances are great that the process is still active. In only 6 of our 19 cases of rheumatic heart disease in which the diagnosis was made clinically were there pathologic stigmata of rheumatic activity.

Despite the severity of the cardiac lesions, however, it is quite apparent that they played a comparatively minor role in the clinical picture except as a late manifestation, and also as a mode of death. Cardiac symptoms were relatively unimportant or were nonexistent

throughout the major part of the lives of these patients. It was not the heart disease, but the joint disease, for which they first sought medical attention. Eventually, however, congestive failure supervened in the majority of cases, but, as has been previously mentioned, at a much later age than is usual in patients with rheumatic heart disease without rheumatoid arthritis. The restricted life imposed on such patients because of their joint deformities probably is responsible for the degree of longevity achieved.

Kast[1] and Pribram[2] differentiated "primary" from "secondary" chronic polyarthritis, stating that, in the former, cardiac involvement was less frequent and usually played an unimportant role if present. In the secondary form, they found that the cardiac involvement was quite often marked, and might dominate the entire clinical picture. Barjon,[16] however, found that the incidence of heart disease was 21 per cent in the former, and 20.5 per cent in the latter, type. Judging from his sixty-two cases and other reports[11, 12, 14, 15] in the French literature, he concluded that no difference existed. Our observations are in agreement in this respect.

The fact that a history of frank rheumatic fever was obtained in only three cases fails to support the concept that, in those cases of rheumatoid arthritis in which heart disease is also found, rheumatic fever had at one time been present. It must be admitted, however, that the absence of such a history is not necessarily too significant. In view of the frequency of the cardiac lesions, however, this point is, at best, of little practical significance, and resolves itself into one of nomenclature rather than etiology. No fundamental purpose is served by separating the two rheumatic diseases, and the issue would be clarified by grouping both under the term "rheumatic state," especially since the cause is unknown in both. It is well known that rheumatic fever is protean in its manifestations and in its course. The addition of the "rheumatoid" cardiac manifestations thus adds to, rather than detracts from, such a concept.

It is interesting to speculate upon the varied vulnerability of the heart and joints, and upon the apparent reciprocal relationship. When one structure is greatly involved, the other is relatively, or absolutely, spared. This variability of tissue response to the same noxious agent has been observed in various disease states. In rheumatic fever, Gross[38] has ascribed the low incidence of valvular involvement in older people to the regressive changes in the musculature and vessels of the valves, resulting in a comparative avascularity. Whether this explanation is purely morphologic, or whether it depends on an as yet unexplained immunologic response, is still to be ascertained.

SUMARY AND CONCLUSIONS

A post-mortem study of 38 cases of chronic rheumatoid arthritis revealed cardiac lesions in 33, in 25 of which (65.7 per cent) the process

was considered to be rheumatic in origin, and of a nonspecific infectious nature in the remaining 8. An active rheumatic process was present in only 6 cases. A history of rheumatic fever was obtained in only 3 cases, and of probable rheumatic fever in 2 others. In 18 patients the arthritis was insidious and progressive, and, in 15, acute attacks of polyarthritis occurred during the course of the disease. The extremely high incidence of rheumatic heart disease in rheumatoid arthritis which was found in this and previous pathologic studies suggests an extremely close relationship which should lead to consideration of the possibility that they may be manifestations of the same underlying disease process.

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COARCTATION OF THE AORTA: CLINICAL AND ROENTGENOLOGIC ANALYSIS OF THIRTEEN CASES

CAPT. LAWRENCE PERLMAN, M.C., ARMY OF THE UNITED STATES

COARCTATION of the aorta is a congenital anomaly which presents interesting clinical and radiological diagnostic features. The developmental anatomy has been well described many times, particularly by Abbott,[1] and any repetition would be superfluous. It is divided into two types, namely, the infantile type, which occurs in children up to the age of 1 year, and the adult type. It is with the latter type that we are concerned.

The incidence of the condition has been estimated to be 1 in 1,500 cases by Blackford,[2] who based his figures on a series of 68,300 routine autopsy reports. Evans[3] found 26 cases of coarctation of the aorta in 19,217 routine necropsies at the Baron Institute of Pathology, London. This included both the infantile and the adult type. There were 11 cases of coarctation of the adult type in 16,215, or an incidence of 1 in 1,471. Levine[4] estimates that 0.1 per cent of the entire population have this anomaly.

The incidence of coarctation in our series was much lower, i.e., approximately 1:10,000. This was in a series of routine physical examinations for army service upon an unselected group of men between the ages of 18 and 35 years. A number of the men were over 35 years, but the percentage of these was so small as to be almost negligible.

Why there is such a great discrepancy between the number of cases noted in routine necropsy reports and the number diagnosed on routine physical examination is difficult to explain. The pathologist can include in his series cases of slight narrowing of the aorta at the site of the ductus arteriosus. In such cases there are no physical signs, and radiological examination shows nothing abnormal. An example may be found in the report by Hallock and Hebbel[5] of the nonclinical type of coarctation. Their patient had no hypertension. The diagnosis was made from the cardiac examination only, and, on autopsy, a slight constriction of the aorta at the point of attachment of the ductus arteriosus was found. In addition to this nonclinical group of cases, there have undoubtedly been some in which the diagnosis was not made. King[6] commented on the fact that only one case of coarctation of the aorta was diagnosed from the time of the founding of the Johns Hopkins Hospital to 1923. In discussing a series of eight cases in which the diagnosis was made clinically, Lewis[7] commented on the number of times some of the patients were examined before the correct

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diagnosis of coarctation of the aorta was made. The majority of the cases which he reported were in men who were examined and pronounced fit for active service in World War I, and showed no symptoms of cardiac disease for some years after their discharge from the British Army.

CASE REPORTS

CASE 1.—The patient, a 28-year-old white man, with no previous knowledge of heart disease, had indulged moderately in athletic activities.

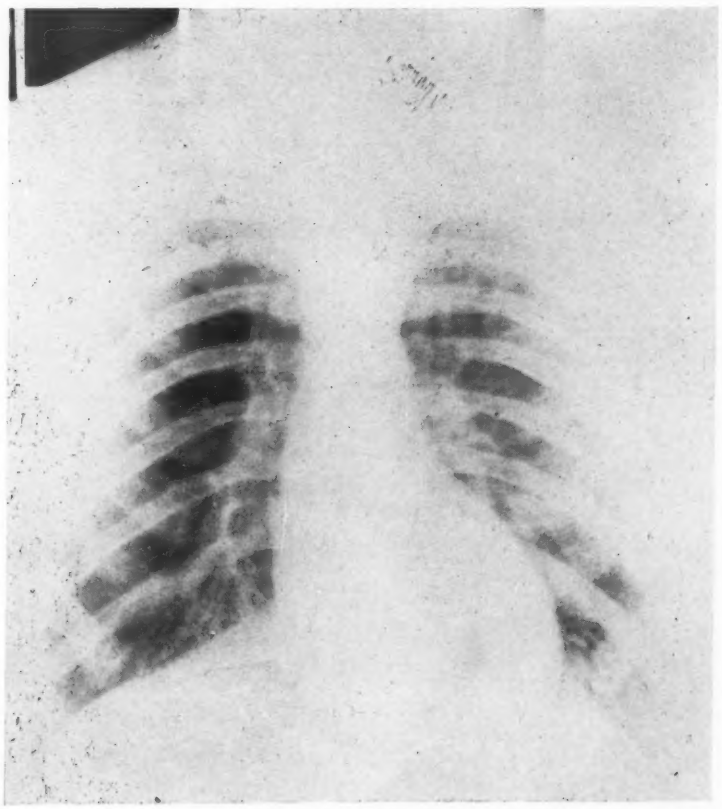

Fig. 1.—Case 1.

Examination revealed a well-developed and well-nourished young man without cyanosis or marked flushing of the face. Carotid pulsations were evident, but not marked. The heart was not grossly enlarged; the apex beat was within the left midclavicular line. Auscultation revealed a harsh, loud, blowing diastolic murmur over the aortic valve and Erb's point. The blood pressure was 200/40. The abdominal aortic and femoral artery pulsations were absent. The blood pressure was not obtainable in the popliteal region. The intercostal vessel pulsations were slight, i.e., they were obtainable only upon extreme pressure on the inferior margins of the ribs.

CASE 2.—The patient was a 21-year-old white man, with no previous knowledge of heart disease. He had led the normal life of a boy and young man and had participated in various types of athletics, but never strenuously.

Examination revealed a well-developed and well-nourished young man. His complexion was normal. The carotid artery pulsations were absent.

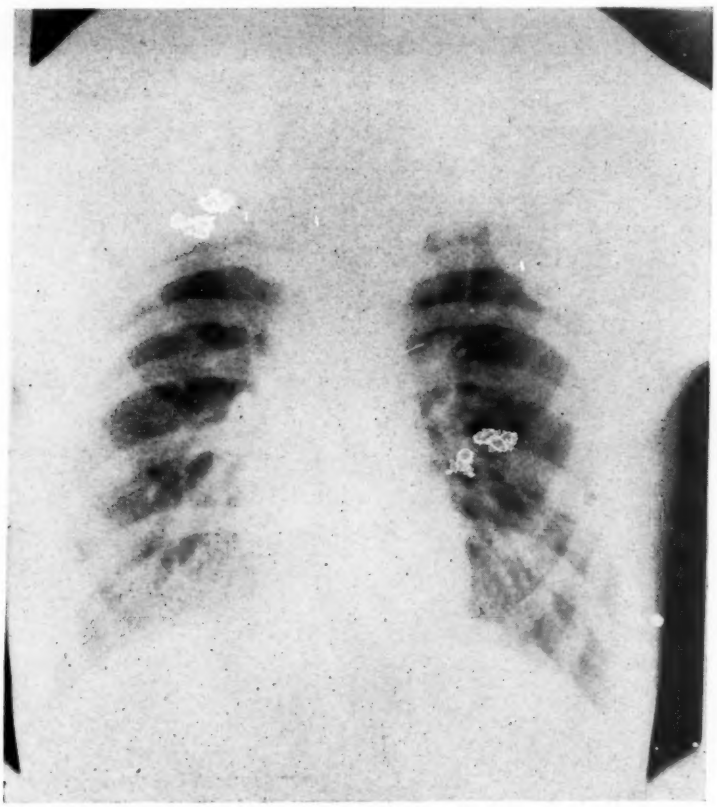

Fig. 2.—Case 2.

The apex beat of the heart was well within the left midclavicular line at the fifth intercostal space. A loud diastolic murmur was heard over the entire precordium; it was most intense at the base of the heart. The blood pressure was 188/88. Abdominal aortic pulsations and femoral artery pulsations were not obtainable. The intercostal vessels were dilated and easily palpable, and, in the right interscapular region, a large vessel was found.

CASE 3.—The patient was a 21-year-old white man who had never been aware of heart disease. No history of athletic endeavor was obtained.

Examination revealed a fairly well-developed, slightly emaciated, young man. His face was of normal color. No carotid pulsation was noted. The cardiac apex was within the left midclavicular line in the fifth intercostal space. Auscultation revealed no murmur, but merely an accentuation of the aortic tones. The blood pressure was 180/110.

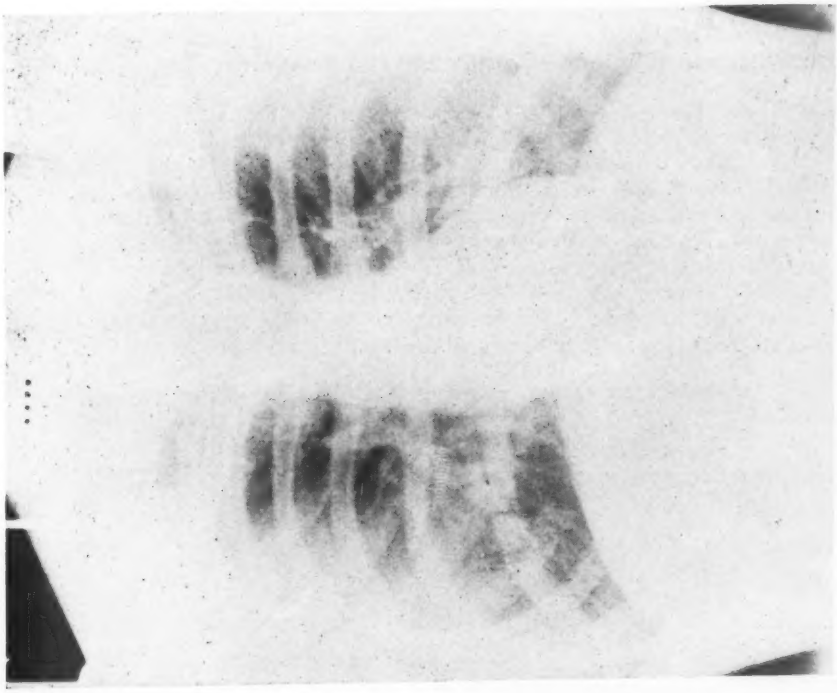

Fig. 4.—Case 4.

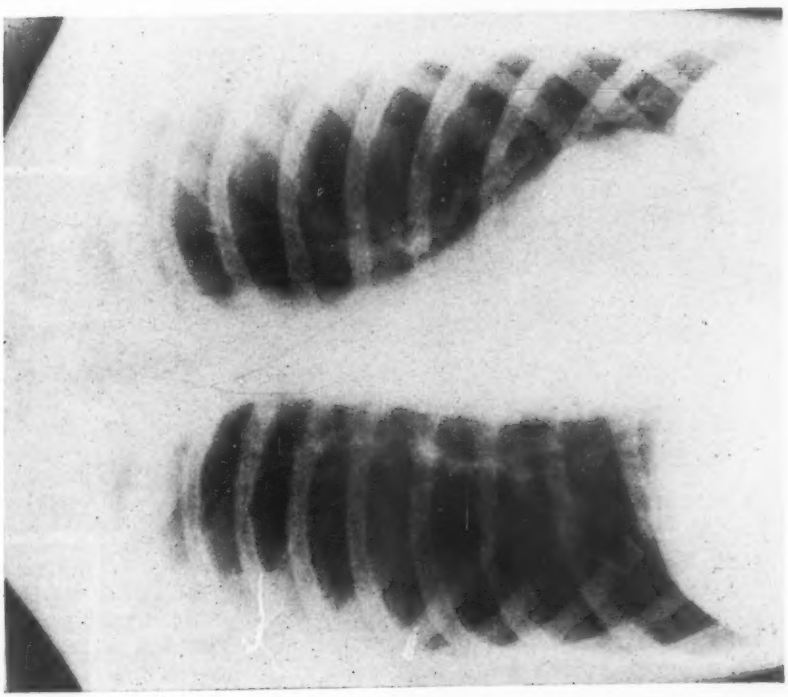

Fig. 3.—Case 3.

Slight pulsation of the abdominal aorta and the femoral arteries was observed. The blood pressure in the popliteal area was 110/80. Moderately strong pulsations of the intercostal vessels were palpated.

CASE 4.—The patient was a 19-year-old white man from whom no previous history of heart disease was elicited. No recreational history was obtained.

Examination revealed a moderately well-developed young man. No abnormal color of the face was noted. The carotid pulsations were marked. The apex of the heart was well within the left midclavicular line at the fifth intercostal space. No cardiac murmurs were heard. The blood pressure was 210-80. The femoral artery pulsations were entirely absent. The blood pressure in the popliteal area was 80/40. Marked pulsations of the intercostal blood vessels were noted.

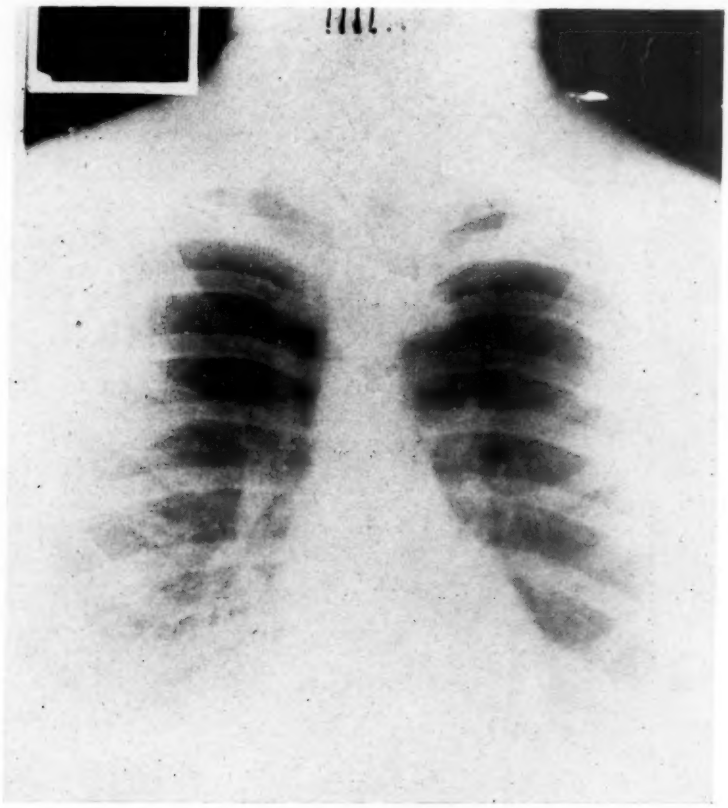

Fig. 5.—Case 5.

CASE 5.—The patient was a 22-year-old white man who had been aware that he had some heart trouble since the age of 14 years. Despite this knowledge, he had played high school and semiprofessional basketball, and had run in the 440-yard dash on his high school track team.

Examination revealed a small, well-built young man. There were marked pulsations of the carotid arteries. The cardiac apex was within normal limits. Auscultation of the heart revealed a loud, blowing, diastolic murmur at the aortic valve and at Erb's point. The blood pressure

was 210/90. Femoral artery pulsations were not obtainable. The blood pressure in the popliteal area was 130/80. Moderate pulsations of the intercostal blood vessels were palpated. The electrocardiogram was normal.

CASE 6.—The patient was a 21-year-old white man who had known that he had a cardiac lesion since early childhood. Five years before the present examination he was told he had high blood pressure. Because of this he had not engaged in any strenuous activities, but felt no discomfort on ordinary activity.

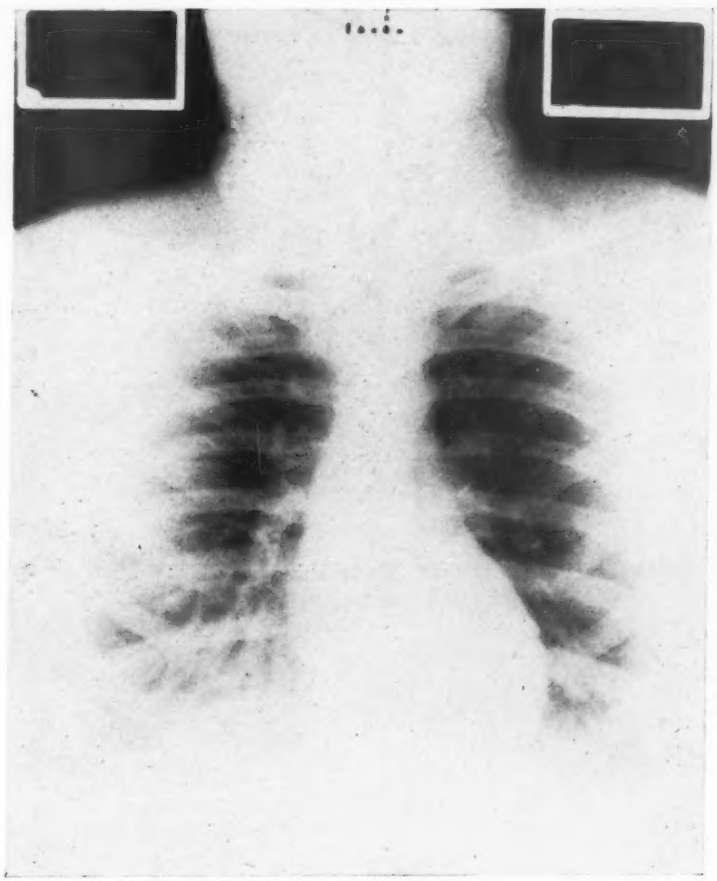

Fig. 6.—Case 6.

Examination revealed a well-developed young white man. The carotid artery pulsation was slight. The heart was not enlarged to physical examination. A soft systolic murmur was heard over the entire precordium, and a low-pitched, diastolic murmur was heard at the aortic valve and at Erb's point. The blood pressure was 170/70. The femoral artery pulsations were not obtainable. The blood pressure in the popliteal area could not be measured. The intercostal blood vessels were palpable upon moderate pressure on the inferior surfaces of the ribs. The electrocardiogram was normal.

CASE 7.—The patient was a 20-year-old white man with no previous knowledge of any cardiac lesion; he gave a history of moderate indulgence in athletic activities.

Examination revealed a well-developed young man. There were moderate pulsations of the carotid arteries. The cardiac apex was 2 cm. to the left of the midclavicular line in the fifth left intercostal space. A loud, blowing, diastolic murmur was heard over the aortic valve and Erb's point. The blood pressure was 220/90. Palpation of the femoral arteries revealed no pulsations, and the blood pressure in the popliteal area could not be obtained. The intercostal vessels were easily palpated, and gave a strong impulse which coincided with cardiac systole.

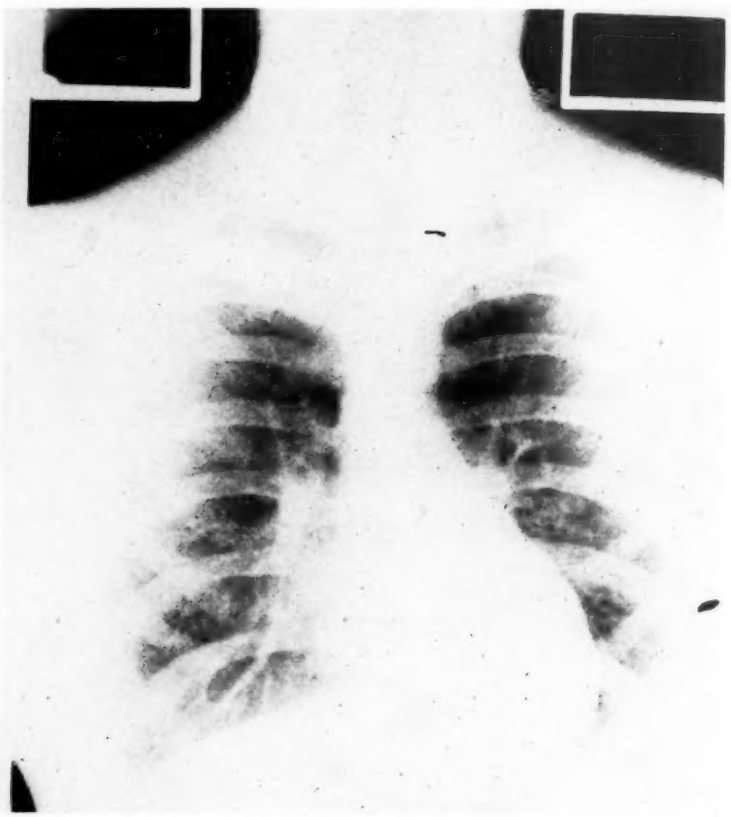

Fig. 7.—Case 7.

CASE 8.—The patient was a 20-year-old white man who had known since the age of 11 years that his blood pressure was elevated. His activity had been limited since early childhood because of a nervous ailment. Two years earlier he had been told that he had coarctation of the aorta, after examination at a large Midwestern medical clinic.

Examination revealed a slightly built, thin young man. The carotid arteries did not pulsate. The heart was not enlarged. No cardiac murmurs were heard. The blood pressure was 160/106. The pulsation of the femoral artery could be felt, but the impulse was of lesser intensity than that of the radial pulse. The blood pressure in the popliteal region was 96/62. The intercostal pulsations were of moderate intensity.

CASE 9.—The patient was an 18-year-old white man with no previous knowledge of cardiac abnormality. He gave a history of active participation in athletics, particularly football, and, to a lesser degree, basketball.

Examination revealed a well-built young man with a ruddy complexion. The carotid arteries could not be seen to pulsate. The cardiac apex was 3 cm. to the left of the midclavicular line in the fifth intercostal space. A loud diastolic murmur was heard at the cardiac apex, the aortic valve, and over Erb's point. The blood pressure was 240/160. The femoral pulsations could not be obtained. The blood pressure in the popliteal area was 140/100. Palpation of the intercostal vessels showed a moderately intense pulsation. The electrocardiogram was normal.

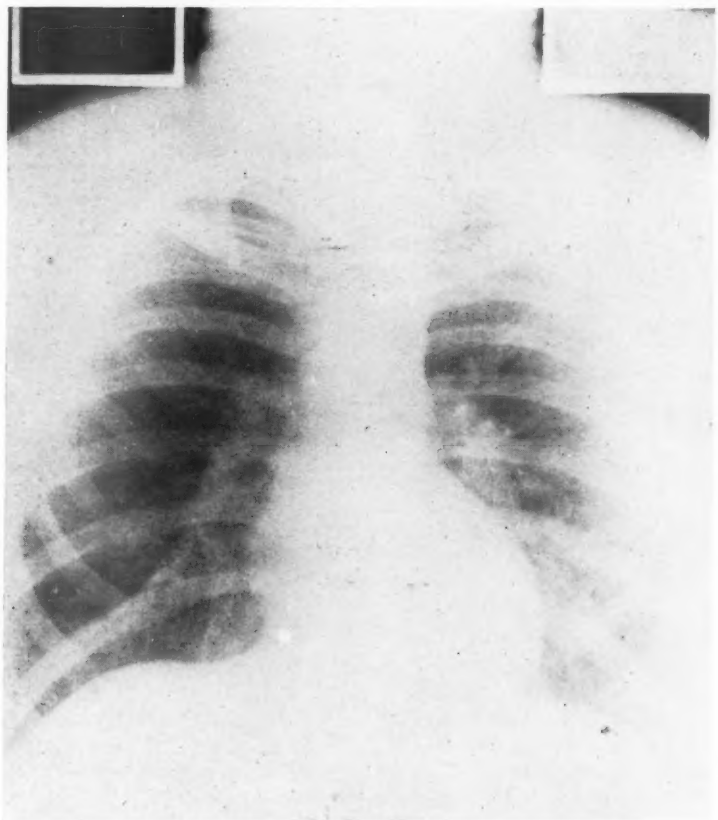

Fig. 8.—Case 8.

CASE 10.—The patient was a 23-year-old white man who had been aware that he had a cardiac lesion since the age of 8 years. Despite this knowledge he had indulged moderately in athletics, including football, boxing, and baseball.

Examination revealed a very well-developed, well-nourished young man. The carotid arteries were pulsating forcibly. The cardiac apex was in the fifth intercostal space in the left anterior axillary line. There was a loud, diastolic murmur at the aortic valve and over Erb's point.

The blood pressure was 184/60. The femoral arteries could not be palpated, and the blood pressure in the popliteal region was not obtainable. The intercostal blood vessels were easily palpable. The electrocardiogram showed a pattern compatible with hypertensive heart disease.

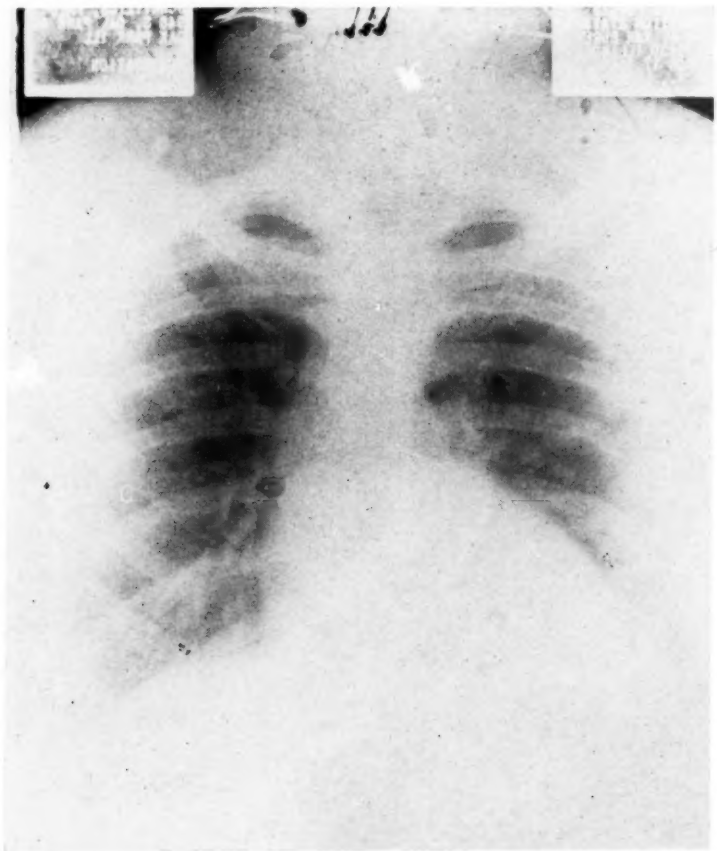

Fig. 9.—Case 10.

CASE 11.—The patient was a 32-year-old white man who had been told that he had hypertension at the age of 22 years. His earlier history showed moderate participation in athletics, and, even after he learned that he had high blood pressure, he had been performing heavy manual labor.

Examination revealed a fairly well-built, young, white man with a very flushed face. The carotid arteries were pulsating strongly. The cardiac impulse was within the midclavicular line in the fifth left intercostal space. Auscultation revealed a soft, blowing, diastolic murmur over the aortic valve which was transmitted to Erb's point. The blood pressure was 214/128. The femoral arteries gave only a moderate impulse to palpation. The blood pressure in the popliteal area was 126/100. The intercostal vessels were easily palpated, and stood out as dilated, wormlike threads over the lateral and posterior aspects of the thorax. The electrocardiogram was normal.

CASE 12.—The patient was a 25-year-old white man who had known that he had some cardiac abnormality since early childhood. Because of this knowledge he had led a very restricted life, and had never indulged in any competitive sports or performed any strenuous physical tasks.

Examination revealed a well-developed, well-nourished, young white man. The carotid arteries were pulsating with moderate intensity. The cardiac apex was within normal limits. Auscultation revealed a harsh systolic murmur at the apex and at the base of the heart. The aortic second sound was markedly accentuated. The blood pressure was 192/70. The pulsations of the femoral artery could not be obtained, and the blood pressure in the popliteal area also could not be obtained. The intercostal vessels could be palpated upon slight pressure on the under surfaces of the ribs. The electrocardiogram showed a pattern compatible with hypertensive heart disease.

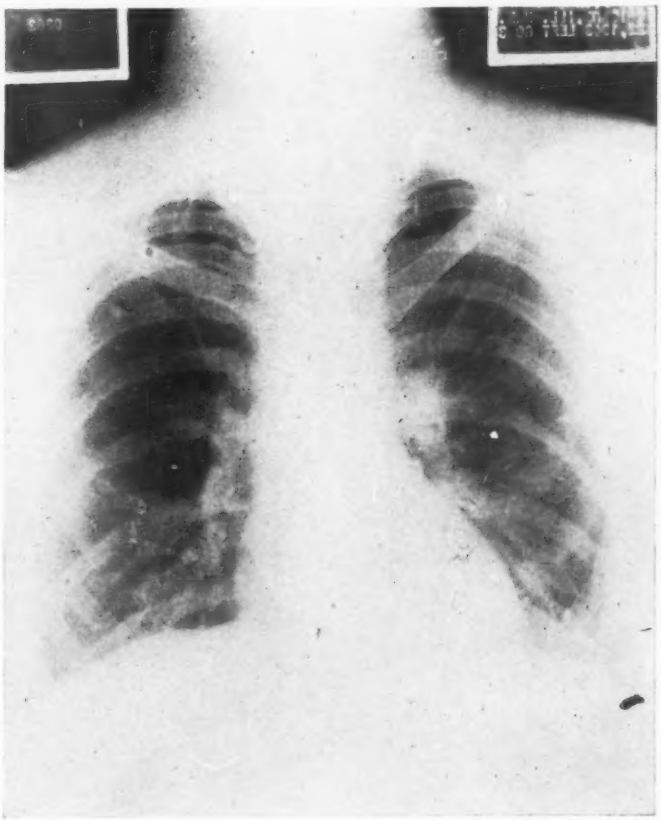

Fig. 10.—Case 11.

CASE 13.—The patient was an 18-year-old white man with no previous knowledge that he had cardiac disease. He gave a history of moderate indulgence in sports, particularly swimming and baseball.

Examination revealed a well-developed, moderately well-nourished, young white man. The carotid arteries were seen to pulsate with moderate intensity. The cardiac apex was in the fifth intercostal space at the

Fig. 12.—Case 13.

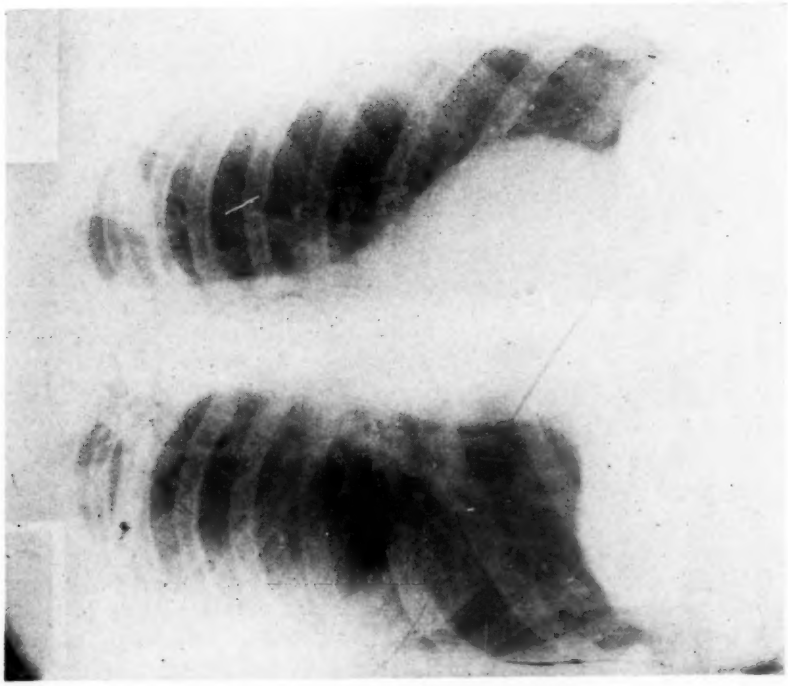

Fig. 11.—Case 12.

left midclavicular line. Auscultation revealed a soft, blowing diastolic murmur at the base of the heart. The blood pressure was 180/90. The femoral artery pulsations were not obtainable, and the blood pressure in the popliteal region could not be measured. The pulsations of the intercostal vessels could be felt with moderate ease. The electrocardiogram was normal.

DISCUSSION

Various methods for the clinical diagnosis of coarctation of the aorta have been advocated. King,[6] in 1926, wrote that pulsation in the interscapular region was the dominant sign of the condition. He stated that the chief value of the roentgenogram was to rule out aneurysm of the aorta. In a later article,[8] he reaffirmed this view by stating that the demonstration of collateral circulation is the most important single clue to the diagnosis of coarctation of the aorta.

In 1932, Dock[9] reported three cases of coarctation of the aorta, and stated that the condition should be looked for in young and middle-aged men with hypertension or hypertension and aortic insufficiency who had pronounced carotid artery pulsations; he advised simultaneous palpation of the femoral and radial pulses, for the femoral pulse is delayed and differs in quality from that in the arms.

In the following year Eppinger and Mittelfart[10] stated that the pathognomonic signs of coarctation of the aorta were a harsh, blowing, systolic murmur over the interscapular region to the left of the spine, heard less intensely over the precordium, and palpable and occasionally visible pulsations over the thorax.

In the same year, Lewis[7] published a series of nine cases of coarctation of the aorta which had been collected over a period of twelve years. In eight of these cases the patients had been seen and the diagnosis had been made clinically, while one was a post-mortem specimen only. He stated, "Of the clinical signs that can be regarded as distinctive there are but two; one is the presence of characteristic anastomotic vessels; the other is the relative weakness and delay of the pulse in the lower limbs. Palpation of the femoral pulse forms and can form no part of a routine examination; it is only undertaken for definite reasons, as when coarctation of the aorta is already suspected, when signs of abdominal aneurysm have been found, or where there are symptoms of inadequate blood flow to the legs. If the diagnosis is to be made it would be wise to examine, as a routine, the femoral pulse in all cases of continued high brachial blood pressure."

Of the thirteen cases here presented, it will be noted that in only three were there pulsations of the femoral artery. In only one of these three cases was the femoral impulse of moderate intensity, and even in this one the impulse did not approach the intensity of the radial artery pulsation. In the remaining two cases the femoral artery pulsation might be classed as slight.

The explanation for the diminution or absence of the femoral pulsation, although blood flow to the lower extremity is present, is well ex-

plained by Bonnet (quoted by Abbott[1]). He states that sensation to the finger does not depend upon blood volume, but on the sharp repercussion of the wave that passes along as the blood is propelled into the aorta. When sudden and abrupt, as normally, the tactile sensation is that of a forcible pulsation. When blood reaches the aorta through a large series of small collaterals, the ascent will be more gradual and the pulse below it correspondingly weaker.

From Table I it might appear that, since intercostal pulsations were present in varying degree in all the cases of coarctation, this would be a better index of the presence of a stenosing aortic lesion. However, intercostal and interscapular vessel pulsations have been noted in cases of uncomplicated aortic insufficiency, and even in extreme tachycardia with or without hypertension. The bounding impulse in the superficial vessels of the thoracic cage in these conditions is not unlike that in many cases of coarctation. Of course, the dilatation and tortuosity of the intercostal vessels do not occur, whereas they are found in well-marked cases of coarctation.

TABLE I

ANALYSIS OF CLINICAL OBSERVATIONS

CASE	AGE (YEARS)	CARDIAC ENLARGEMENT	MURMUR	BLOOD PRESSURE		PULSATIONS	
				BRACHIAL	POPLITEAL	FEMORAL	INTERCOSTAL
1	28	None	Diastolic, base	200/40	0	None	Slight
2	21	None	Diastolic, entire precordium	188/88	0	None	Moderate
3	21	None	None	180/110	110/80	Slight	Moderate
4	19	None	None	210/80	80/40	None	Marked
5	22	None	Diastolic, base	210/90	130/80	None	Moderate
6	21	None	Diastolic, base	170/70	0	None	Slight
7	20	Moderate	Diastolic, base	220/90	0	None	Moderate
8	20	None	None	160/106	96/62	Moderate	Moderate
9	18	Moderate	Diastolic, entire precordium	240/160	140/100	None	Moderate
10	23	Marked	Diastolic, base	184/60	0	None	Moderate
11	32	None	Diastolic, base	214/128	126/100	Slight	Marked
12	25	None	Systolic, entire precordium	192/70	0	None	Moderate
13	18	None	Diastolic, base	180/90	0	None	Moderate

The predominant cardiac murmur was the basal diastolic murmur. This was present in nine of the thirteen cases. Of the remaining cases, no cardiac murmur was heard in three, and a systolic murmur was present in one. The explanation of the presence of the diastolic murmur in such a large number of cases in the present series is difficult. Certainly, it cannot be explained wholly as the result of a bifid aortic cusp, for Abbott's[1] statistics reveal an incidence of only 25.1 per cent of bifid aortic cusps in one hundred eighty-three cases of coarctation of the aorta. Using this as a standard, we should expect, at the most, three patients to have a diastolic aortic murmur. Table I reveals six more than this anticipated number of diastolic aortic murmurs. The possibility of a concomitant rheumatic valvulitis may be considered,

but, in view of the absence of any history of rheumatic fever in these cases, this is unlikely. Perhaps the great pressure within the portion of the aorta proximal to the stenosis, which causes dilatation of the aorta itself, also causes stretching of the aortic ring, with resultant separation of the commissures of the aortic valve and the production of aortic insufficiency.

Although the diagnosis of coarctation of the aorta may be made clinically, the roentgenogram is a very definite diagnostic aid. In some cases the diagnosis may be only hazarded on clinical grounds, and confirmatory evidence from the roentgenogram is essential. The diagnostic value of the roentgenogram in this condition was not realized until the report of Railsback and Dock,[11] in 1929. This was followed, in 1930, by the report of Fray,[12] who also pointed out the value of the roentgenogram in the diagnosis of coarctation of the aorta.

There is a characteristic radiological syndrome consisting of:

1. Absence of the aortic knob.
2. Dilatation of the ascending and transverse portions of the arch of the aorta.
3. Erosion of the lower margin of the posterior portions of the ribs.
4. Roundness or enlargement of the left ventricle.

TABLE II

ANALYSIS OF RADIOLOGICAL OBSERVATIONS

CASE	AORTIC KNOB	AORTIC DILATATION	RIB EROSION	HYPERTROPHY LEFT VENTRICLE
1	Absent	Slight	Moderate	None
2	Absent	Moderate	Slight	None
3	Absent	None	Moderate	None
4	Absent	Moderate	Moderate	None
5	Absent	Slight	Moderate	Slight
6	Absent	Slight	Slight	Slight
7	Absent	None	Slight	Moderate
8	Absent	Moderate	Slight	Moderate
9	Absent	Slight	Slight	Moderate
10	Absent	Moderate	Moderate	Marked
11	Absent	Moderate	Marked	Slight
12	Absent	Slight	Moderate	Slight
13	Absent	None	Moderate	Slight

In the present series the only constant radiological signs were absence of the aortic knob and erosion of the ribs (Table II). The patient with the slightest amount of rib erosion was the one with the lowest blood pressure in the series (Case 8; B.P. 160/106). This coincides with a statement of King,[8] who believed that erosion of the ribs is not necessarily present in typical coarctation of the aorta, and, in the case he cited, the blood pressure was only 123/87. Dilatation of the aorta was found in ten cases of the series. The contour of the left ventricle was normal in four cases, slightly enlarged in five cases, moderately enlarged in three, and markedly enlarged in one. This change in left ventricular contour coincided neither with the degree of elevation of the blood pressure nor with the type of murmur.

Electrocardiograms were obtained in seven of the cases. Five of these were normal, and the remaining two were compatible with hypertensive heart disease. As a diagnostic aid, it would seem that the electrocardiogram is of very little value. The changes observed probably depend directly upon the response of the myocardium to the long-continued strain of blood pressure elevation. This seems likely because the abnormal electrocardiograms occurred in the two cases of longest duration (Cases 11 and 12).

SUMMARY

1. The incidence of coarctation of the aorta is discussed, and the relation of post-mortem and clinical incidence is compared.

2. Thirteen cases of coarctation of the aorta are reported.

3. The clinical manifestations and the constance of these manifestations, as previously reported, are correlated.

4. The roentgenologic and electrocardiographic observations in these cases are analyzed.

CONCLUSIONS

1. Coarctation of the aorta should be suspected in all cases of hypertension, or hypertension and aortic insufficiency.

2. These patients should be examined for absence of femoral artery pulsation or a marked diminution in the strength of the femoral pulsation. Secondarily, an attempt should be made to palpate the intercostal vessels.

3. The significant roentgenologic abnormality is absence of the aortic knob, with confirmatory evidence in the form of rib erosion, aortic dilatation, and left ventricular enlargement.

The author wishes to thank Major G. Pelkey and Capt. H. Pritchard for their aid in obtaining the roentgenograms.

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ELECTROCARDIOGRAPHIC STUDY OF LATERAL INFARCTION, PROVED AT AUTOPSY

CARL F. SHAFFER, M.D.
OMAHA, NEB.

A PREVIOUS paper from the Henry Ford Hospital reported a series of patients with coronary artery occlusion, proved at autopsy, and correlated their electrocardiographic features with the location of the myocardial infarct.[1] These, with additional cases since then, have been reviewed for the purpose of distinguishing the graphic variations associated with lateral, as distinguished from anterior and posterior, infarction.

Other authors have demonstrated the relation of the electrocardiogram to the site of the infarct on the anterior or posterior surface of the left ventricle; Barnes[2] has aptly discussed this subject. The subdivision of the electrocardiogram of myocardial infarction into anterior and posterior types is useful for general diagnostic purposes, and its value would undoubtedly be increased by the addition of a third, or lateral, type to this group.

A number of studies have been made relating to the situation of myocardial infarctions, but, since the incidence of uncomplicated lateral infarcts is small, the electrocardiographic information in proved cases is meager; there are definite reasons for this.

As pointed out by F. J. Smith and his associates, the type of case at autopsy is, in the majority of instances, one of ancient and multiple infarctions, with or without superimposed, recent, single infarction. Judging from our studies, instances of recent single infarction are in the minority. Sprague and Orgain[3] have reported a similar experience in their review of autopsies at the Massachusetts General Hospital. They state that, "Since it is a group such as ours that lives long enough to be studied by the practicing physician it becomes the more important that we discover what such cases show clinically by the electrocardiogram and at autopsy."

The distribution of the coronary arteries to the myocardium is subject to a great number of variations.[4] In general, infarction of the anterior apical surface of the left ventricle is usually produced by occlusion of the anterior descending branch of the left coronary artery; infarction of the posterior basal surface is usually produced by occlusion of the posterior descending branches of the right coronary; and infarction of the lateral midventricular surface is usually produced by occlusion of the circumflex branch of the left coronary artery. Septal

From the Department of Medicine, Henry Ford Hospital, Detroit, Michigan.
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infarcts may occur with occlusion of the septal branches of the left or right coronary arteries, or as part of an anterior or posterior infarct.

Occlusion of the anterior descending branch of the left coronary artery is more common than that of the posterior descending branches of the right coronary artery. Occlusion of the circumflex branch of the left coronary is the least common of these, probably, as suggested by Whitten,[5] because of the position of its first part in the coronary sulcus and above the ventricle. Furthermore, in addition to usually supplying the lateral surface of the left ventricle, branches of this artery may supply the anterior apical or, more frequently, the posterior basal part.[4] Occlusion of the left circumflex is variously reported to occur with an incidence of 5 to 10 per cent. It therefore becomes apparent why uncomplicated lateral infarction is not common.

MATERIAL STUDIED

For the past twenty years the electrocardiograph has been available for use on our patients. During this period approximately 200 persons with cardiac infarction have been examined post mortem. Two conditions reduce the number of cases of completely reliable material for electrocardiographic correlation. First, coronary occlusion may occur without producing myocardial infarction if there is an adequate collateral circulation, or coronary insufficiency, without actual occlusion, may occur and produce infarction if there is transient ischemia. Second, in a large general hospital, several different pathologists will have dictated the protocols with no consistent method of description of coronary or myocardial disease.

In the material studied there were five instances of recent, uncomplicated infarction of the lateral surface of the left ventricle. Infarcts described as extending to either the apical, anterior, basal, or posterior surfaces were excluded. Histologic description of the infarcts confirmed their recent occurrence when this was not established clinically.[6] In all but one there was complete obstruction of the left circumflex artery, and the remaining had no demonstrable occlusion.

A review of the records gave electrocardiographic information on all of these patients, as described in the case reports. The precordial leads were made with the precordial electrode at the cardiac apex, (IV F), and are presented in all instances according to the method recommended by the Committee of the American Heart Association for the Standardization of Precordial Leads.[7] Those illustrated were rephotographed and printed in reverse; the others, as described, required no transposition for this purpose, for they were originally made by the present standard method.

CASE REPORTS

Case 1.—T. H., a white man, aged 42 years, was admitted to the hospital Feb. 3, 1933, twenty-four hours after the onset of severe substernal pain. He had been having mild chest pain on effort for the previous two weeks. His initial temperature was 98° F., his pulse rate, 80, his respirations, 20, his blood pressure, 150/100, and his leucocyte count, 12,500. The electrocardiogram made the same day was normal except for left axis deviation; no precordial lead was obtained. He had a recurrence of pain forty-eight hours later, and the next day there were a

slight relative elevation of the RS-T segment in Lead I, a depression of the RS-T segment in Lead III, and an inverted T wave in Lead IV. On the seventh day a diphasic T in Lead II and an inverted T in Lead III had developed; the inverted T persisted in Lead IV.

The clinical course was uneventful until, three weeks later, there were another attack of pain, a further fall in blood pressure, and the appearance of a pericardial friction rub. The next day there was inversion of the T wave in Lead I, with a return of upright T waves in Leads II and III and a further inversion of the T in Lead IV. Seven days later an inverted T wave in Lead II had developed. During the ensuing three weeks he had frequent, transient, chest pain and progressive

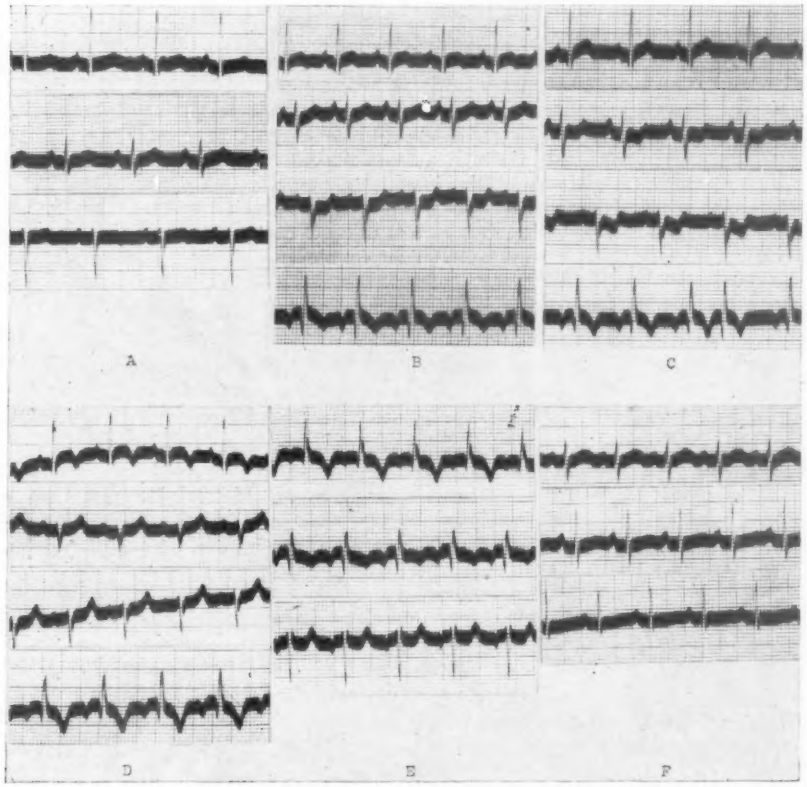

Fig. 1.—Electrocardiograms in Case 1. *A*, Tracing made on first hospital day twenty-four hours after onset of pain. *B*, Fourth day. *C*, Seventh day. *D*, Twenty-eight day. *E*, thirty-fifth day. *F*, Sixty-fifth day.

congestive heart failure. Digitalis was given and brought about slight temporary improvement, but the disease proved fatal on the sixty-sixth hospital day. The standard leads shortly before death were not definitely abnormal. There was no axis deviation or abnormal Q waves, and the T waves in Leads I and II were upright with an isoelectric T in Lead III (Fig. 1).

At autopsy the heart weighed 650 grams. Immediately distal to the origin of the left circumflex an organized thrombus occluded the artery. Further in its course there were more recent thrombi. On the lateral

surface of the left ventricle there was a large, dilated aneurysmal sac, measuring 10 cm. in diameter, whose wall was composed in part by the adherent visceral and parietal pericardium.

CASE 2.—J. H., a white man, aged 55 years, was admitted March 12, 1938, one week after the occurrence of substernal pain of several hours' duration, with a complaint of shortness of breath. The temperature was 100° F., the pulse rate, 120, the respirations, 40, the blood pressure, 110/80, and the leucocyte count, 11,250. Examination revealed mild congestive heart failure. The electrocardiogram showed slight left axis deviation, large Q waves in Leads II and III, an elevated RS-T segment in Leads I, II, and IV, and an inverted T wave in Lead IV. He received no digitalis. Death occurred the next day.

At necropsy the heart was hypertrophied and weighed 900 grams. A recent thrombus completely occluded the left circumflex artery. There was a soft, hemorrhagic area of infarction approximately 10 cm. in diameter on the lateral surface of the left ventricle. The pericardium around this was covered with a fibrinous exudate.

CASE 3.—W. H., a white man, aged 37 years, entered the hospital March 28, 1928, complaining of nausea and vomiting during the previous ten days. There had been no chest pain or symptoms of myocardial insufficiency. The temperature was 98.6° F., the pulse rate, 100, the respirations, 18, and the blood pressure, 250/130. There were a moderately severe secondary anemia and a 4 plus albuminuria, with hyaline casts. The nonprotein nitrogen content of the blood was 240 mg. per 100 c.c. The clinical diagnosis was chronic nephritis with uremia. A routine electrocardiogram showed left axis deviation and an inverted T wave in Lead 1. No precordial lead was obtained. Coma preceded death on the seventh day.

Post mortem, the heart weighed 500 grams. Recent thrombosis of the left circumflex artery, had caused a necrotic infarct "several square centimeters in diameter" on the lateral surface of the left ventricle. The pericardium was covered with a fibrinous exudate.

CASE 4.—C. M., a white woman, aged 53 years, was admitted June 4, 1928, forty-eight hours after the onset of substernal pain. There had been no previous angina of effort. The initial temperature was 98° F., the pulse rate, 100, the respirations, 25, the blood pressure, 125/80, and the leucocyte count, 13,750. Examination revealed mild congestive heart failure. The electrocardiogram showed no axis deviation, a large Q wave in Lead III, and an elevation of the RS-T segment in Lead III, with corresponding depression of the RS-T segment in Lead I. There was no precordial lead. The patient died in an attack of pulmonary edema on the fourth day. She had received no digitalis.

At autopsy the heart weighed 450 grams. A recent, organizing thrombus occluded the left circumflex artery, and a soft, hemorrhagic infarct (unmeasured) occupied the lateral surface of the left ventricle.

CASE 5.—M. E., a white woman, aged 60 years, entered the hospital April 25, 1941, with complaints of shortness of breath and palpitation. There was no history of chest pain. Her symptoms had become more pronounced a few days before admission. She had received digitalis for the previous month. The temperature was 98.6° F., the pulse rate, 80, the respirations, 30, the blood pressure, 160/95, and the leucocyte count, 18,000. The patient had moderate congestive heart failure. The

electrocardiogram substantiated the diagnosis of auricular fibrillation, and showed slight left axis deviation, low voltage of the QRS complexes, and absence of the R wave in Lead IV. Death from progressive heart failure occurred on the seventh day.

At necropsy the heart weighed 550 grams. There was extensive coronary atherosclerosis, but no actual occlusion, with a recent infarct, 5 cm. in diameter, on the lateral surface of the left ventricle.

COMMENT

Electrocardiographically, one can usually recognize patterns of anterior or posterior myocardial infarction, although in numerous instances there are indeterminant features, or these do not indicate the location of the infarct. This may be due to one or more of several factors: the position of the heart in the thorax, the condition of the circulation to the myocardium, the occurrence of previous or multiple infarction, the situation of the infarct in relation to the endocardial or epicardial surfaces, the development of pericarditis with or without effusion, the association of conduction defects, modification by digitalis therapy, and the number of the electrocardiograms and the time at which they were taken in relation to the occurrence of the infarct.

The anterior type is recognized by the development of a prominent Q wave in Lead I, early elevation of the RS-T segment in Lead I, with reciprocal depression of this segment in Lead III, later inversion of the T wave in Lead I, and elevation of the RS-T segment, with later inversion of the T wave, in Lead IVF. In the posterior type there are a prominent Q in Lead III and frequently in Lead II, early elevation of the RS-T segment in Lead III, with reciprocal depression in Lead I, and later inversion of the T in Lead III, or Leads II and III. With posterior infarction the precordial lead is less likely to change, but, if it does, there is usually depression of the RS-T segment, with the T wave remaining upright.

When infarction involves both the anterior and posterior surfaces of the left ventricle, the effect of the anterior one predominates in the electrocardiogram, as reported by Wolferth, Wood, and Bellet.[8]

Recently these authors[9] have reported a series of cases wherein they defined a lateral type, characterized by depression of the RS-T segment in Leads I and II (commonly, although not universally present), absence of signs of infarction in Lead III, and depression of the RS-T segment in the precordial lead. Their conclusion, based on one case of uncomplicated lateral infarction, proved at autopsy, with a second probable case, was that lateral infarction does occur anatomically, and that, since characteristic anterior and posterior types exist, it is reasonable to suppose that there is a lateral type, also.

Not one of our autopsy cases presented these features, nor was there a single consistent pattern. In Case 1, with serial electrocardiograms, there were the features of both anterior and posterior types, with a predominant anterior pattern. It is interesting to note that the standard

leads on the day before death were not definitely abnormal. Case 2 resembled Case 1 in that there was a mixed anterior and posterior pattern. Case 3 was of a definite anterior, and Case 4 of a definite posterior, type. In Case 5, in which there had been previous digitalis medication, there was no clinical evidence of recent infarction. This patient also had auricular fibrillation, an arrhythmia that Wood and his associates say occurred with unusual frequency in their cases.

The literature contains information on the correlation of autopsy observations with electrocardiograms. There is usually no special reference to the type of pattern associated with lateral infarction. A summary of a group of these investigations, wherein such infarcts are described, is presented in Table I. In most instances the corresponding electrocardiograms are noted as conforming to one type or another without further elaboration. When these are stated to be atypical and are more completely described, there is no conformation to a "lateral type." However, as reported by Wood, et al., the electrocardiographic features of the acute lesion may subside very rapidly and become unrecognizable.

TABLE I

SUMMARY OF REPORTS BY VARIOUS AUTHORS LISTED AMONG THE REFERENCES*

AUTHOR (REFERENCE) NUMBER	TOTAL NUMBER OF CASES	TOTAL NUMBER OF LATERAL INFARCTS	AGE OF INFARCTS: OLD	AGE OF INFARCTS: NEW	ELECTROCARDIOGRAM TYPE: ANTERIOR	POSTERIOR	ATYPICAL	NORMAL
10.	168	3	?	?	1	2		
11.	149	2	1	1	2			
3.	131	2	1				2	
			1 combined					
12.	34	1		1				1

*This summary represents the number of autopsy cases, the number of lateral infarcts with electrocardiographic study, and the electrocardiographic pattern. The atypical patterns were associated with defects in conduction: in one, auricular fibrillation, in the other, intraventricular block.

SUMMARY

1. There is a small incidence of fresh, uncomplicated infarction of the lateral surface of the left ventricle, as ascertained by a study of autopsy cases.

2. There was no characteristic electrocardiographic pattern associated with lateral infarction analogous to anterior and posterior types in our series of cases.

The autopsy records were reviewed with Richmond W. Smith, M.D., Detroit, Michigan.

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ADDENDUM

Since this article was submitted, a discussion of the subject by Thomson and Feil has been published.[13] They presented a larger number of cases of lateral infarction, and their conclusions were in favor of a typical electrocardiographic pattern as proposed by Wood, Wolferth, and Bellet. In their group with "typical" electrocardiograms, as presented, Case 1 had a depressed S-T segment in Leads I, II, and IVR, and Case 2, a depressed S-T segment in Lead IVR. The remaining two cases in this group could have been included in their group of lateral infarctions with "atypical" electrocardiograms, for both had abnormalities consistent with a mixed anterior and posterior pattern.

THE EFFECT OF DRUGS ON THE SURFACE CAPILLARIES OF THE MACACA RHESUS

RUDOLPH H. PELZER, M.D., AND WALTER REDISCH, M.D.
NEW YORK, N. Y.

INTRODUCTION

THE recording of over-all vascular responses gives little information concerning the changes occurring within a specific portion of the peripheral circulation. An attempt is made here to indicate the direct or reflected responses of the capillaries, as such, to certain drugs. Direct observation of the capillaries in various sites on the human skin has been widely used. Evaluation of the observations is difficult because of the lack of standardization in recording them, and in the maintenance of a fixed experimental environment. Since capillary microscopy permits direct observation of the changes in the most distal portion of the vascular tree, it holds obvious advantages as an approach to the study of the responses of the capillaries to drugs.

When a capillary is viewed by direct microscopy in vivo, with the magnification of 60 and 100 times which we employed, the endothelial tube limiting the capillary cannot be distinguished. The capillary is seen because of the blood contained within it. Variations in the diameter of the column of blood due to drugs or other causes are actually the alterations which are interpreted as changes in the diameter of the capillary.

It becomes possible, therefore, in observing a given field, to ascertain the morphology of the capillaries present and the nature of the blood flow within them. Differentiation between arterial and venous limbs of the capillaries is made possible by the difference in diameter and the direction of blood flow. A small segment between the arterial and venous limbs, of greater diameter than either, may frequently be distinguished, and is called the "transitional limb."

METHOD

Four female macaques, varying in weight between 4.5 and 5.5 kg., were used. The observations were made on the capillaries of the skin at the base of the fingernail in the right forelimb.

The widespread physiologic influences which affect the peripheral capillaries can be interpreted at present only to a limited degree. Control was attempted for the following factors:

1. Diet was held constant for four weeks prior to the first observations, and was maintained fixed.

From the Department of Anatomy, New York University College of Medicine.

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2. Fluid intake was fairly constant, in that the monkeys were offered 400 c.c. of water per day, of which 300 to 400 c.c. were consumed.

3. The room temperature was maintained between 25° and 30° C. during observations.

4. Observations without anesthesia were attempted by the use of wide arm sleeves to fix the limbs firmly and not impair the circulation. Because of changes due to struggling, and possible psychogenic changes, it was found necessary to employ a general anesthetic. This was given as nembutal intraperitoneally in doses which varied between 0.55 and 1.2 c.c. per kilogram of body weight; the smallest dose which would produce anesthesia was used in each case.

The state of the sexual cycle was not given special consideration, for the observations were concerned essentially with relative changes during the given experiment.

In order that the hand would be held in a fixed position most favorable for access to the fingernail bed, a dental compound glove was molded to the hand of each monkey and employed during observation. These gloves covered the hand from above the wrist to the base of the terminal phalanges, but did not impair the circulation. The hairs of the fingers which overlapped the field of observation were cut with scissors. The area was cleansed by wiping with cedar oil.

The anesthetized animal in each instance was placed in the semiprone position with the right arm extended at approximately heart level and the hand encased within the compound glove. Observations were carried out with a Leitz capillary microscope at magnifications of 60 and 100 times. Photographs were taken in some instances, using a Leica camera equipped with a beam-splitting mechanism. The light source was a 6-volt, 5-ampere lamp encased in an air-cooling system, and the light was passed through a green and a yellow Corning heat-absorbing glass filter. This setup, as checked by direct thermometry, gave only slight changes in temperature at the site of observation. With a thermometer placed horizontally, and the mercury base at the point of greatest light concentration and coinciding with the position of the monkey's finger during observations, there were changes of 1.4° and 1.1° C. in five minutes and six minutes, respectively.

Since the method is subjective, and open to the errors inherent in such an approach, all experiments were repeated at least twice and observations were made independently by the writers.

The different drugs were administered only by direct intravenous injection into the superficial leg veins; 1 c.c. was the largest quantity of fluid given at a single injection.

OBSERVATIONS

Four series of observations on the effects of nembutal anesthesia were made; the monkey was fully anesthetized in three, and remained partially responsive in the fourth. The capillary loops showed slight blurring and minor diameter changes, such as slight narrowing of the arterial limbs and slight widening of the venous limbs.

Sterile saline in 1 c.c. doses, of pH 5.9, was injected intravenously in two instances. No changes in diameter or stream were noted.

1. Drugs considered to act on the parasympathetic nervous system.

A. *Pilocarpine.*—Four series of observations with intravenous

doses of 0.5 mg. of pilocarpine showed a consistent narrowing of the venous limbs, and either a slight slowing or no change in the blood flow. Narrowing of the arterial limbs was noted in one of these observations.

B. *Acetyl-β-Methylcholine.*—Eight series of observations with intravenous doses of acetyl-β-methylcholine, varying from 0.25 to 2 mg., showed consistent changes in the indistinctness of the capillary outline, widening of the arterial and venous limbs, and marked slowing of the stream. "Fading" of the capillary outline occurred within one-half minute after doses of 1 mg. and over, and was followed by return of capillary visibility and the previously mentioned changes.

C. *Atropine.*—Twelve series of observations with intravenous doses of atropine sulfate are reported, two of which followed pilocarpine injection. When given alone in eight instances, in doses varying between 0.5 and 5 mg., there were a consistent, slight widening of the transitional limb, and occasional widening of the venous and arterial limbs. In two instances, with doses of 0.25 mg., the only change was a slight narrowing of the arterial limbs. Marked widening of the entire capillary loop followed the administration of atropine thirty-five minutes after pilocarpine had been given, and, in another instance, thirty-nine minutes after pilocarpine, atropine produced marked widening of the venous and transitional limbs with but slight widening of the arterial limb.

2. Drugs considered to act on the sympathetic nervous system.

A. *Epinephrine.*—Sixteen series of observations were made after the intravenous injection of epinephrine hydrochloride in doses varying from 0.0002 to 0.5 mg.

a. A dose of epinephrine of 0.001 mg., or over, induced complete blanching and disappearance of the capillaries in the field. With return of the capillary to view, markedly narrowed venous and transition limbs were first noted, followed soon after by reappearance of similarly narrowed arterial limbs.

b. A dose of epinephrine of 0.00075 to 0.0003 mg. induced narrowing of the arterial limbs, followed by narrowing of the venous and transition limbs. The stream of blood was slowed.

c. A dose of 0.0002 mg. of epinephrine produced no change in the capillary loops.

B. *Ergot group.*—Five series of observations are reported with ergotamine, ergonovine, and ergotoxine.

a. In two instances, after the injection of 0.25 and 0.50 mg. of ergotamine, the capillaries showed narrowing of the arterial limbs, fluctuations in distinctness of outline, and slowing of the stream.

b. In two instances, after injections of 0.20 mg. of ergonovine, there were narrowing of the arterial limbs and fluctuating distinctness of the capillary outline.

c. In one instance, after the injection of 0.50 mg. of ergotoxine, there were narrowing of varying degree of the arterial limbs and fluctuating distinctness of the capillary outline.

3. Miscellaneous.

A. *Nicotinic acid.*—Doses of 5 mg. and 10 mg. of nicotinic acid were administered intravenously. The smaller dose was found to give a slight widening of the entire capillary loop, and the large dose induced a more marked widening of the arterial limb.

B. *Nicotamic acid.*—A dose of 5 mg. of nicotamic acid, in injected intravenously, induced an increased speed of blood flow and widening of the entire capillary loop.

TABLE I

SUMMARY OF EFFECTS OF SPECIFIC DRUGS ON THE SURFACE CAPILLARIES OF THE MACACA RHESUS

DRUG	ART. L.	TRANS. L.	VEN. L.	BL. FLOW
Pilocarpine	Nar.		Nar.	Dec.
Acetyl-β-Methylcholine	Wid.		Wid.	Dec.
Atropine	Wid.	Wid.	Wid.	
Epinephrine	Nar.	Nar.	Nar.	Dec.
Ergot	Nar.			Dec.
Nicotinic acid	Wid.	Wid.	Wid.	Inc.

Art. L. = Arterial limb of the capillary.
Trans. L. = Transitional limb of the capillary.
Ven. L. = Venous limb of the capillary.
Bl. Flow = Blood flow through the capillary.
Nar. = Narrowed capillary limb.
Wid. = Widened capillary limb.
Dec. = Decreased blood flow.
Inc. = Increased blood flow.

DISCUSSION

Capillary blood vessels are described histologically as tubes about 8 micra in diameter, formed by a single layer of endothelial cells, and in which muscle elements are lacking. Intercellular cementing substance is interposed along the margins of the endothelial cells.[1] Rouget cells,[2, 3] which are believed to represent specialized contractile elements, are distributed at intervals along the capillaries. The blood flow is from the arterial to the venous limb of the capillary loop. Arteriovenous anastomoses, with muscular walls and rich autonomic innervation, are abundant in the fingers and palm of the hand, and act as special sluice gates to by-pass the capillary bed.

For direct capillary microscopy in man, the capillaries of the skin and accessible mucous membranes are utilized. In the region of the fingernail bed (at the base of the cuticle) and the inner surface of

the lip, observation of longer capillary limbs is possible because they tend to lie horizontal to the external surface.

In three of the four monkeys studied, the capillary forms at the fingernail bed showed meandering of the limbs, shorter arterial limbs, and venous limbs, and close proximity to the subpapillary plexus. These capillaries resembled the inhibited developmental form, or "archicapillary," described in man by Jaensch,[4] and are similar to those in cases of mongolism[5] and pituitary disturbances of the Fröhlich type.[6-8] The fourth monkey had capillary loops of hairpin shape, closely similar to the so-called human capillaries in the same region.

Reference to the table in the preceding section, summarizing the effects of the drugs on the capillaries, indicates their possible division into two main groups. Epinephrine, pilocarpine, and ergot produced narrowing of the capillaries, whereas atropine, nicotinic acid, and acetyl-β-methylcholine caused widening of the capillaries.

1. Drugs causing narrowing of the capillaries.

Epinephrine in doses sufficient to induce a pressor response acts by direct myocardial stimulation, increased heart rate, and by constriction of the arterioles.[9, 10] The range of doses employed in this study, i.e., 0.0003 mg. to 0.5 mg., induced a narrowing of the entire capillary. Reduction of the injected dose in two instances to 0.0002 mg. gave no observable change in the capillaries. With minute doses intravenously in animals or subcutaneously in man, a fall in diastolic pressure caused by vasodilatation has been observed.[11] In the ear of the rabbit, blanching of the capillary fields after the administration of epinephrine was observed by Meltzer and Auer.[12] Subsequent hyperemia of the central vessel and arterioles occurred in some instances, but no mention is made of similar capillary changes. Studies of the capillaries in man after the administration of 1 mg. doses subcutaneously showed narrowing with no subsequent dilatation, although the observation was carried on for over one hour.[13, 14] There is no direct evidence in the literature that capillary widening is caused by epinephrine; the evidence that vasodilatation may occur is based essentially on plethysmographic studies indicating over-all vascular changes in the part,[15-17] and on thermocouple studies indicating temperature changes in the muscle.[18]

The action of pilocarpine on the peripheral circulation has not been extensively investigated. It is difficult to explain the observation reported here of decreased diameter of the capillary limbs and no change or slight decrease in blood flow, rather than the expected peripheral vasodilatation. Although the autonomic responses to pilocarpine are considered to be due to its direct action on cells innervated by postganglionic cholinergic fibers, some apparently anomalous reactions of the cardiovascular system have been reported.[19, 20] It has been suggested by Heaton and MacKeith[21] that the anomalous effects on the circulation may possibly be explained by stimulation of the preganglionic sympathetic fibers by pilocarpine.

Diameter and blood flow changes in the peripheral capillaries at the fingernail bed in man have been reported after the administration of ergotamine tartrate to patients with migraine.[22] The mechanism of the action of ergotamine tartrate is believed to be a stimulation of the myoneural junctions of the motor sympathetic nerves.[23] This action is consistent with the observed capillary narrowing.

2. Drugs causing widening of the capillaries.

Doses of atropine between 0.5 and 5 mg. were found to induce small increases in capillary diameter. With doses of atropine less than 1 mg. there was, in some instances, a decrease in the diameter of the arterial side of the capillary. The action of the drug may be peripheral, as a direct vascular effect. Raymond-Hamet,[24] in studies on dogs, concludes that atropine may act directly on the smooth muscle of vessels or their terminal innervation. Another theory holds that dilatation of cutaneous blood vessels after atropine (atropine flush) is a compensatory mechanism to permit heat loss, and thus offset the rise in temperature which atropine induces because of the suppression of sweat. It has further been considered that atropine flush follows dilatation of arterioles from stimulation of the vasodilator center. Lewis,[25] however, has shown that a "flush," in general, is related to changes in the subpapillary plexus, and not to increased blood flow or diameter of the capillaries. Marrazzi[26] believes that atropine acts at the sympathetic ganglia to block tonic vasoconstrictor effects. The observations reported here with direct microscopy may be correlated satisfactorily with this conclusion. No explanation can be offered for the fact that there was a more marked increase in capillary diameter when atropine was administered subsequent to pilocarpine.

The increased peripheral capillary diameter and increased blood flow after nicotinic acid administration are consistent with the reported clinical observations. Spies and his co-workers[27, 28] have noted the occurrence in man of increased temperature, flushing, burning, and itching after oral or intravenous doses of nicotinic acid, affecting especially the skin of the face and upper part of the trunk. Similar changes have been reported by Atkinson.[29] The mechanism of this nicotinic acid side action is not known, although the reaction is seemingly roughly proportional to the dose.[30]

The observations on acetyl-β-methylcholine reported here, namely, an increase in the arterial and venous capillary limb diameters, are consistent with those recorded in the literature. Doses of 20 mg. in man, administered subcutaneously or intramuscularly, or larger doses by mouth, give a transient fall in blood pressure and the sensation of warmth and flushing.[31] A rise in digital skin temperature has been noted by Goldsmith[32] after oral doses of acetyl-β-methylcholine; a similar rise in skin temperature has been noted after iontophoresis.[33] The portion of the circulatory tree involved in these responses is not specified. An explanation that may be offered for the absence of in-

crease in blood flow through the observed peripheral skin capillaries is the possibility of increased flow through the unobserved arteriolovenous anastomoses.

Diameter changes in capillaries after drug administration may be the result of direct effects on the limbs of the capillaries, or reflections of changes occurring in the arterioles or veins. Widening of the arteriole, when associated with increase in blood flow, may induce passive widening of the arterial capillary limb. Diameter changes of the limbs of a capillary, however, may be due to the resultant balance of vasoconstrictor and vasodilator impulses, or thinning or swelling of the endothelial cells.[34, 35] The method employed here does not yield any definite clue as to which of the mentioned mechanisms may be involved in the change in capillary diameter. These drugs which are known to act on the autonomic nervous system may be considered to transmit their capillary effect over the autonomic pathways.

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ELECTROCARDIOGRAPHIC CHANGES OF IMPENDING INFARCTION, AND THE ISCHEMIA-INJURY PATTERN PRODUCED IN THE DOG BY TOTAL AND SUBTOTAL OCCLUSION OF A CORONARY ARTERY

ROBERT H. BAYLEY, M.D., AND JOHN S. LA DUE, M.D.
NEW ORLEANS, LA.

INTRODUCTORY REMARKS

IN A previous communication[1] we have described the manner in which the electrocardiographic pattern of ischemia and injury may be recorded. When a segment of the anterior descending branch of the dog's left coronary artery is dissected through a small hole in the pericardial sac and a ligature is passed around the artery, the vessel may be occluded totally or subtotally, as desired, by applying tension on the ligature. An essentially unipolar lead is employed, with the exploring electrode placed upon the anterior (or anterolateral) surface of the pericardial sac superjacent to the terminals of the dissected artery, and the indifferent electrode on the left foreleg. The choice of galvanometer terminals is always such that a relatively positive sense of the potential at the exploring electrode, as compared with that at the indifferent electrode, produces an upward movement on the completed record. Continuous recordings are made before, during, and after brief experiments, or at frequent intervals during and after occlusions which last longer than ninety seconds. The resulting electrocardiographic changes are conveniently referred to as the ischemia-injury pattern.[1, 2] It is our present purpose to report the effect on the ischemia-injury pattern produced by subtotal occlusion, and to discuss some of the implications suggested by the modifications of the pattern as they appear to concern certain electrocardiographic problems encountered clinically.

METHOD AND MATERIAL

The method of preparation of the animal was similar to that described in a previous communication.[1] Some refinements are noteworthy, however. A good exposure of the pericardial sac is obtained by dividing one or two costochondral cartilages before the incision is spread open. The cotton foot of the exploring electrode is a thin, circular disc, 1 cm. in diameter, attached to a cotton wick. Only the disc is permitted to touch the animal at the desired region of the pericardial surface. Momentary contacts with the chest wall or with the lung will produce disturbing artifacts on the completed record. In the experiments reported, an accessory lead was recorded simultaneously. The

From the Department of Medicine of the Louisiana State University School of Medicine, New Orleans.
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method of taking the accessory lead varied with the particular preparation. At times it was of the semiunipolar variety, with the exploring electrode in the subcutaneous tissues superjacent to the right ventricle. At other times it was of the essentially unipolar variety, with the exploring electrode placed directly on the pericardial sac over the posterolateral aspect of the left ventricle. In one animal Lead II was recorded simultaneously, and, in another animal, Lead I was used. Twelve young, medium-sized dogs were used, and were sacrificed at the end of four to six hours.

RESULTS

Dogs 10 and 11 died during the course of preparation. Dog 6 developed auricular tachycardia with a rate of 180 per minute. During the course of experimentation with total occlusion,[1, 2] we have had three animals whose hearts acted in a similar way. All yielded atypical occlusion patterns which closely resembled one another. Although we are not prepared to discuss these patterns at the present time, it appears that a high rate of beating is associated with an alteration in the dynamics of coronnary flow which is reflected in ischemia-injury pattern of occlusion. Dog 8 yielded curves of the kind we have interpreted as evidence that the exploring electrode had been placed superjacent to a region of the myocardium not involved during occlusion by the expanding zones of ischemia and injury. This might have been anticipated from previous experience, for in this animal the anterior descending branch was observed to divide early into two subdivisions of approximately equal size. Usually, the inferior subdivision is considerably smaller. Dissection of both subdivisions with simultaneous occlusion of each subsequently yielded satisfactory patterns. The remaining seven animals likewise yielded results of a uniformly predictable character.

Diversion of T in Stages.—The curves displayed in Fig. 1 show a negative T, obtained after arterial dissection, which undergoes gradual reversion after an intravenous injection of 0.12 Gm. of theophylline with ethylenediamine.[2] Shortly after the reversion, subtotal occlusion was carried out in eight stages by intermittently increasing the tension on an elastic band, looped about the dissected artery. A strip was recorded commencing about thirty seconds after each increase in tension. The result is shown in Fig. 2, in which inversion of T is observed to occur in eight stages. The inverted T in Stage 8 is comparable in form to that observed before theophylline reversion (Fig. 1). The interval over which the inversion stages extend is approximately ten minutes. It is recalled that the homologous inversion which follows sudden, complete occlusion[2] is obtained in about thirty seconds. In the last four stages shown in Fig. 2 there is an undulating variation in the amplitude of T which is synchronous with the artificial respiratory movement of the lungs and mediastinum. The smaller T deflections are associated with the taller QRS deflections, and, conversely, the taller T deflections are associated with the smaller QRS deflections. Undulating variations

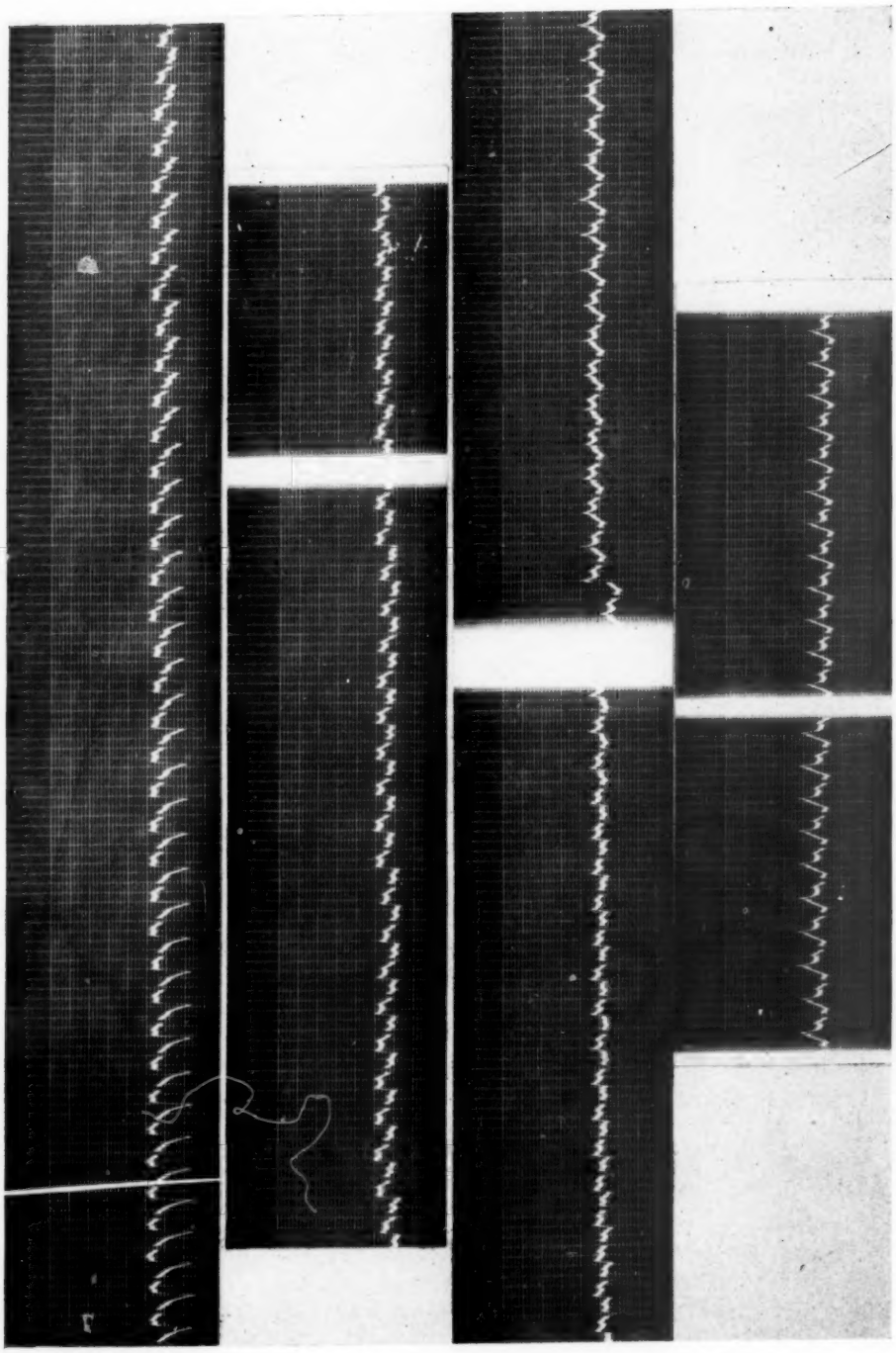

Fig. 1.—An intermittent recording of the reversion of T from a negative to a positive form after the intravenous injection of 0.12 Gm. of theophylline with ethylenediamine. The exploring electrode was in contact directly with the heart's surface 1 cm. above the apex on the anterior wall of the left ventricle. The injection was completed at the time signal in the top strip. The QRS deflections are rapid and hard to make out. R reaches to the top of the strip and S moves off the bottom of the strip. A small Q grows to 4 mm. in amplitude by the end of the recording. The time lines are 0.1 second apart, and the standardization is ½ normal.

are rapid and hard to make out. R reaches to the top of the strip and S moves off the bottom of the strip. A small Q grows to 4 mm. in amplitude by the end of the recording. The time lines are 0.1 second apart, and the standardization is ⅛ normal.

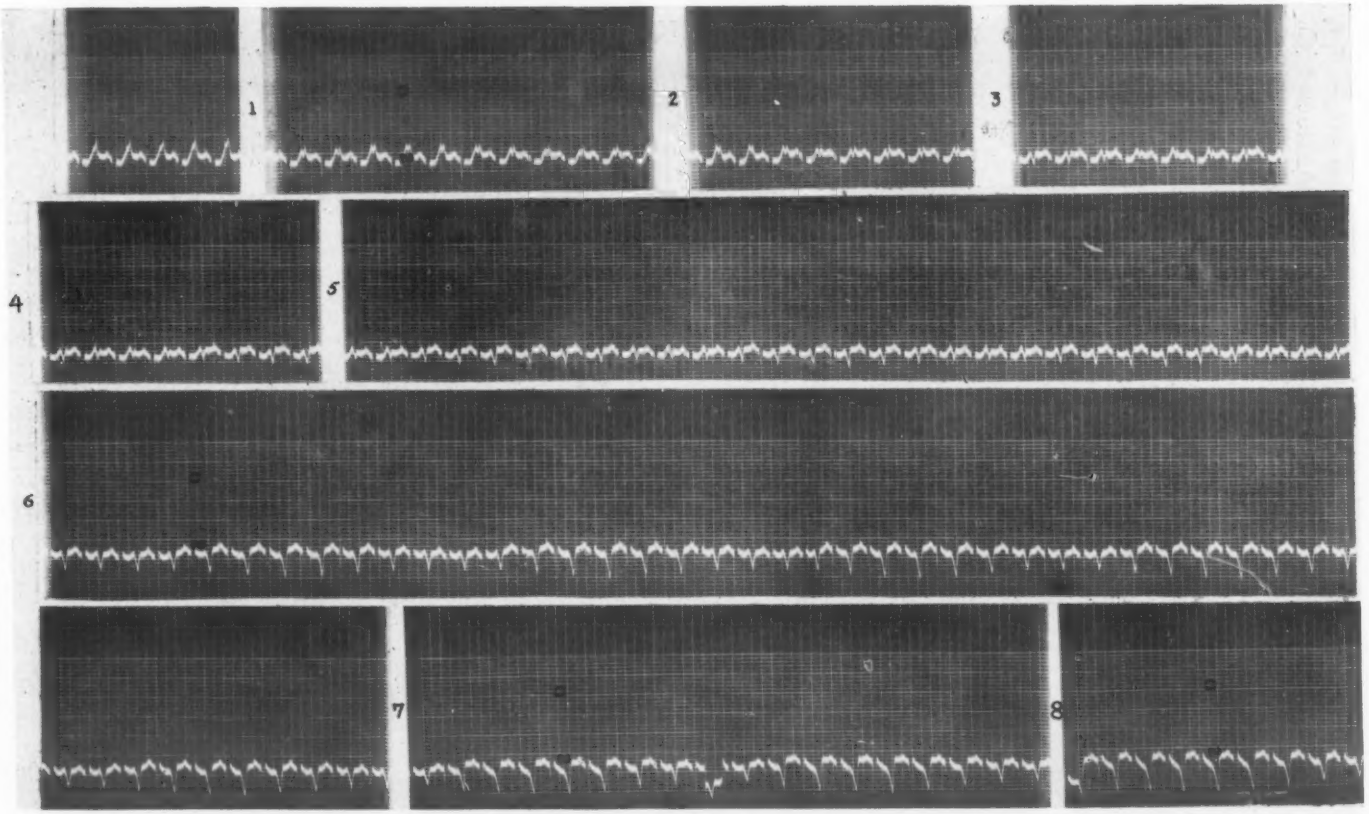

Fig. 2.—A continuation of the experiment started in Fig. 1. Read from above down, and from left to right: First strip is a control before starting subtotal occlusion in eight stages. Before each of the remaining eight strips the elastic ligature was tightened. Note the inversion of T in stages. Note the undulating change in the form of T (synchronous with the respiratory movement). QRS remains practically unchanged throughout. Time and standardization are the same as in Fig. 1.

in the amplitude of QRS which are synchronous with the respiratory movement are observed to occur continuously throughout all of our experiments. They are extracardiac in origin, and are associated with the respiratory variation of the conductivity of the medium surrounding the heart. If the T-wave changes depicted in Fig. 2 are to be ascribed to the same cause, they should be like in kind, and should vary directly with the QRS changes. Actually, the T-wave changes, although they are synchronous with the respiratory movement, are unlike in kind, vary inversely with the QRS changes, and occur only during the subtotal occlusion period. We ascribe the undulating form

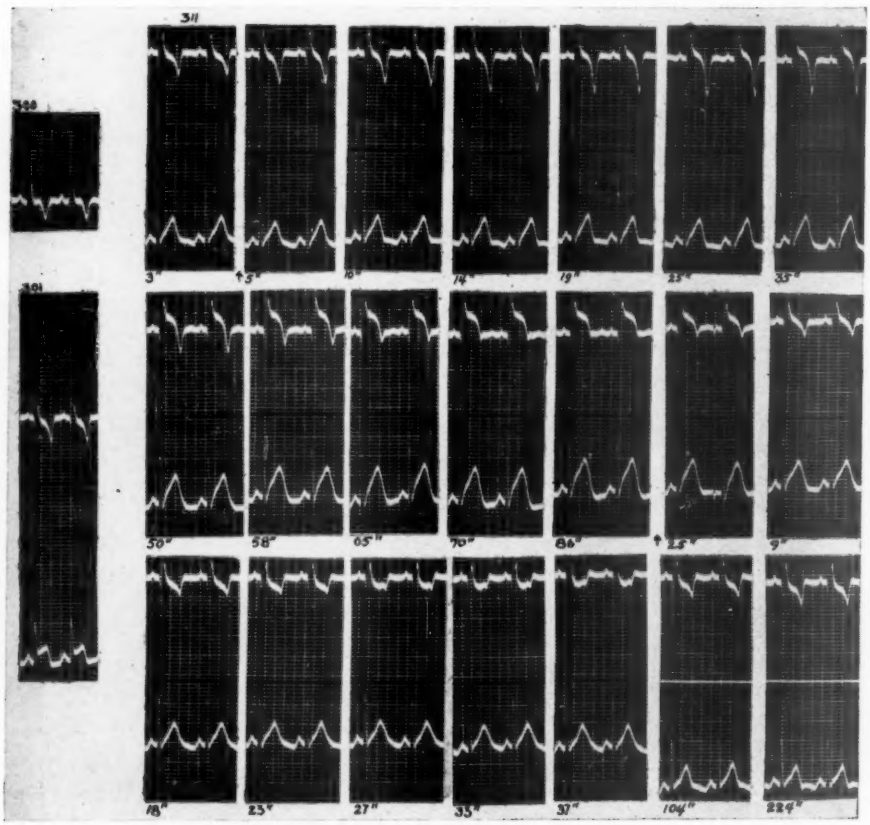

Fig. 3.—Complete occlusion for ninety seconds. Strip *300* is a control recorded before opening the chest. The exploring electrode is in the subcutaneous tissues superjacent to the apex of the left ventricle. Strip *301* is a control taken before arterial dissection. The exploring electrode of the main (top) lead was on the anterolateral aspect of the pericardial sac superjacent to that part of the free wall of the left ventricle irrigated by the artery which is as yet undissected. The exploring electrode of the accessory (bottom) lead was in the subcutaneous tissue superjacent to the free wall of the right ventricle. Reading from left to right and from above down are strips cut from a continuous recording made before, during, and after occlusion of the anterior descending branch of the left coronary artery. The first strip is the postdissection control. The two arrows indicate the times at which occlusion started and ended, respectively. The figure under each strip indicates the time in seconds before occlusion started, after occlusion started, and after occlusion ended, respectively. The pattern of the main lead is a typical negative T pattern. Note that only minor changes appear in the accessory lead. The time lines are 0.1 second apart, and the standardization is ½ normal for the main lead, and normal for the accessory lead. In the main lead the top of the R deflections was sacrificed to conserve space. See text.

of T to the varying degree of subtotal occlusion produced by the rise and fall of the heart with respiration and with respect to the fixed extremity of the elastic ligature.* After release of the subtotal occlusion the inverted T gradually became positive.

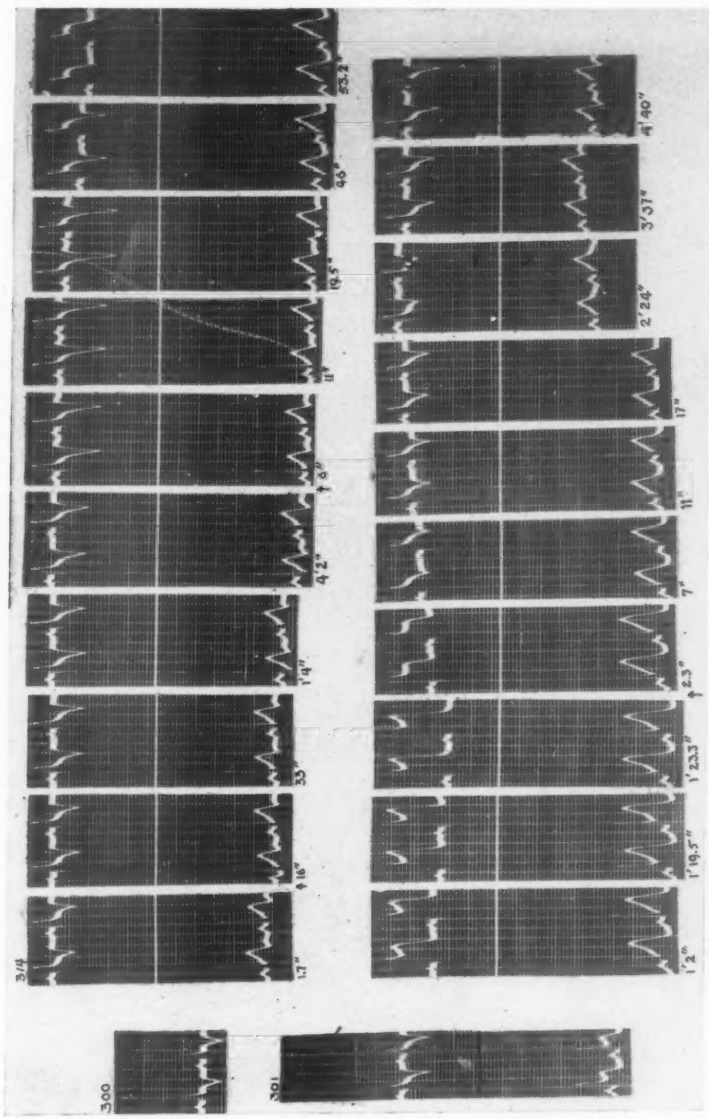

Fig. 4.—A continuation of the experiment commenced in Fig. 3. The two solid rows of strips are, reading from left to right and from above down, from a continuous recording made before, during, and after subtotal occlusion of five minutes' duration and total occlusion for ninety seconds. The three arrows indicate, respectively, the times at which subtotal occlusion started, at which total occlusion started, and at which occlusion ended. The figures under each strip indicate, respectively, the time before subtotal occlusion started, the time after subtotal occlusion started, the time after total occlusion started, and the time after occlusion ended. The dash denotes minutes, and the double dash, seconds. Time and standardization same as for Fig. 3.

Prolonged Diversion of T.—Fig. 3 displays strips which were cut from a continuous recording made before, during, and after ninety seconds of complete occlusion. The exploring electrode of the accessory lead

*This is the only experiment in which an elastic ligature was used, and in which the exploring electrode was placed directly upon the heart's surface.

(lower curve) was superjacent to the anterolateral wall of the right ventricle. The tall R deflections of the upper curve are removed to conserve space. The first arrow indicates the time at which sudden, total occlusion was commenced; the second arrow indicates the time at which the occlusion was released. The ischemia effect was maximum twenty-five seconds after the occlusion commenced. The general form of the pattern is typical of the negative T variety.[1] The animal (Dog 3) was the only one of the series of twelve to display a negative T deflection in the control of the main curve recorded *before* arterial dissection. The accessory lead from the right ventricle displays relatively minor T-wave changes. Fig. 4 shows the electrocardiographic changes that appeared during a five-minute period of subtotal occlusion and during an immediate subsequent period in which the subtotal occlusion was made complete for ninety seconds. The experiment was carried out on Dog 3 several minutes after completion of the experiment shown in Fig. 3. A comparison of Fig. 4 with Fig. 3 shows, therefore, the nature of alterations of the ischemia-injury pattern produced by a complete, ninety-second occlusion with and without an immediately preceding period of prolonged ischemia. Evidently, the effects due to complete occlusion are more pronounced and regress more slowly after occlusion ends if the onset of complete occlusion is immediately preceded by a period of subtotal occlusion.

The Effects of Variable Subtotal Occlusion.—The curves shown in Figs. 5, 6, and 7 represent the effects produced by high-grade subtotal occlusion of five minutes' duration, during which the tension on the ligature was relaxed slightly whenever a definite injury effect appeared in the moving shadow of the galvanometer string. At the end of the five-minute period of subtotal occlusion, the occlusion was made complete for ninety seconds (see time signals in Figs. 6 and 7), after which complete release of the ligature was followed by a return of the curve to a nearly normal form. The accessory lead selected for the preparation (Dog 9) was standard Lead I. The ischemia-injury effects in Lead I, although much smaller in magnitude, are like in kind to those observed in the unipolar lead. Moreover, the order of appearance and disappearance of the changes is the same in the two methods of leading. On the other hand, the time of appearance and disappearance of the changes in the extremity lead, as compared with homologous changes in the unipolar lead, is not in close agreement because effects which have reached striking proportions in the latter are concurrently insignificant in the former type of lead. Other evidence (to be reported later) demonstrates emphatically the unreliability of extremity leads in experiments of the kind under consideration.

DISCUSSION

In 1931, Wood and Wolferth[3] produced brief, complete occlusions of the coronary arteries in dogs and recorded the effects intermittantly with extremity leads. Occasionally, Lead II was recorded continuously.

Certain of their observations and interpretations differ from ours. They observed that the "results of clamping a large coronary become apparent in 15 sec." Unipolar leads demonstrate that the associated electrical changes commence almost at once. They observed further that "occlusion in a healthy fresh heart does not produce electrocardiographic changes as readily (promptly) as it does in a damaged one." We find that the ischemic changes appear immediately, whether or not temporary occlusion (or occlusions) has been previously carried out. They state that "sometimes the experimental occlusion of a large

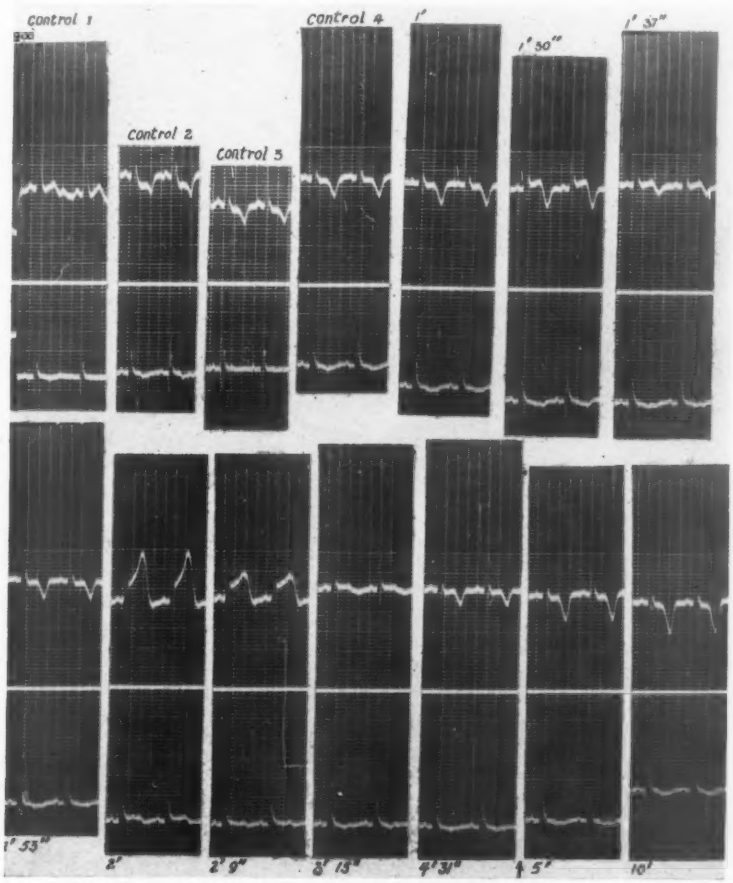

Fig. 5.—The effects of high-grade subtotal occlusion of varying degree for a five-minute period, followed by complete occlusion for ninety seconds. Reading from left to right and from above down: The exploring electrode of the main (upper) lead was on the pericardial sac superjacent to that part of the free wall of the left ventricle normally irrigated by the dissected artery. The accessory (lower) lead is standard Lead I. Controls *1*, *2*, *3*, and *4* are before opening the chest, after opening the chest, after arterial dissection, after warming the pericardium with normal saline, and before occlusion, respectively. The first arrow indicates the interval within which subtotal occlusion was started. The second arrow indicates the interval within which the subtotal occlusion was made complete and during which the continuous strip shown in Figs. 6 and 7 was recorded. The time signal (strip *a*, Fig. 6) indicates the onset of complete occlusion. The time signal (strip *e*, Fig. 7) indicates the end of occlusion. The figures over the strips (top row) and under the strips (bottom row) indicate, respectively, the time after subtotal occlusion started, and the time after total occlusion ended. The dash indicates minutes, and the double dash indicates seconds. Standardization is ⅛ normal and normal for the unipolar and for the extremity lead, respectively. See text.

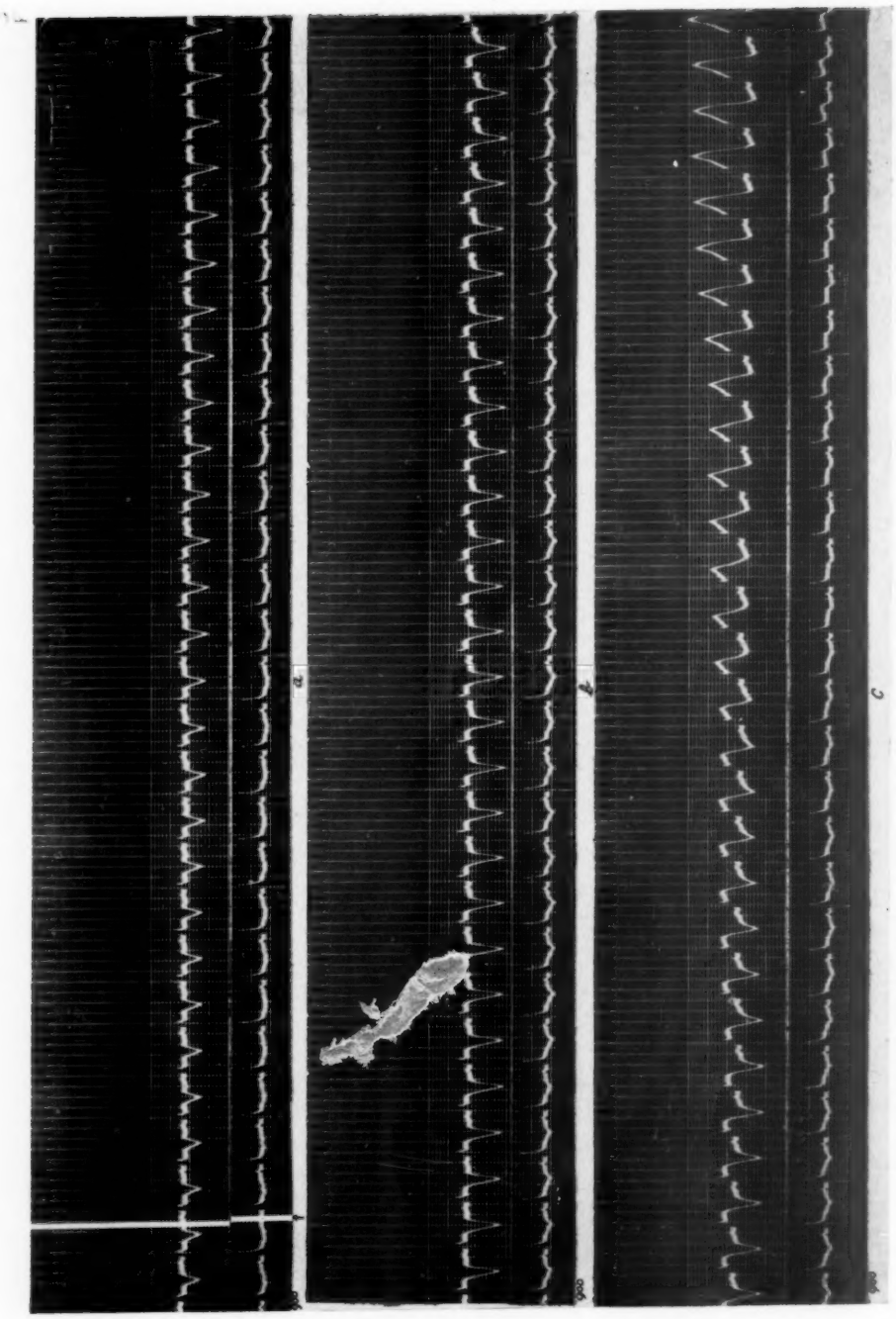

Fig. 6.—See legend of Fig. 5.

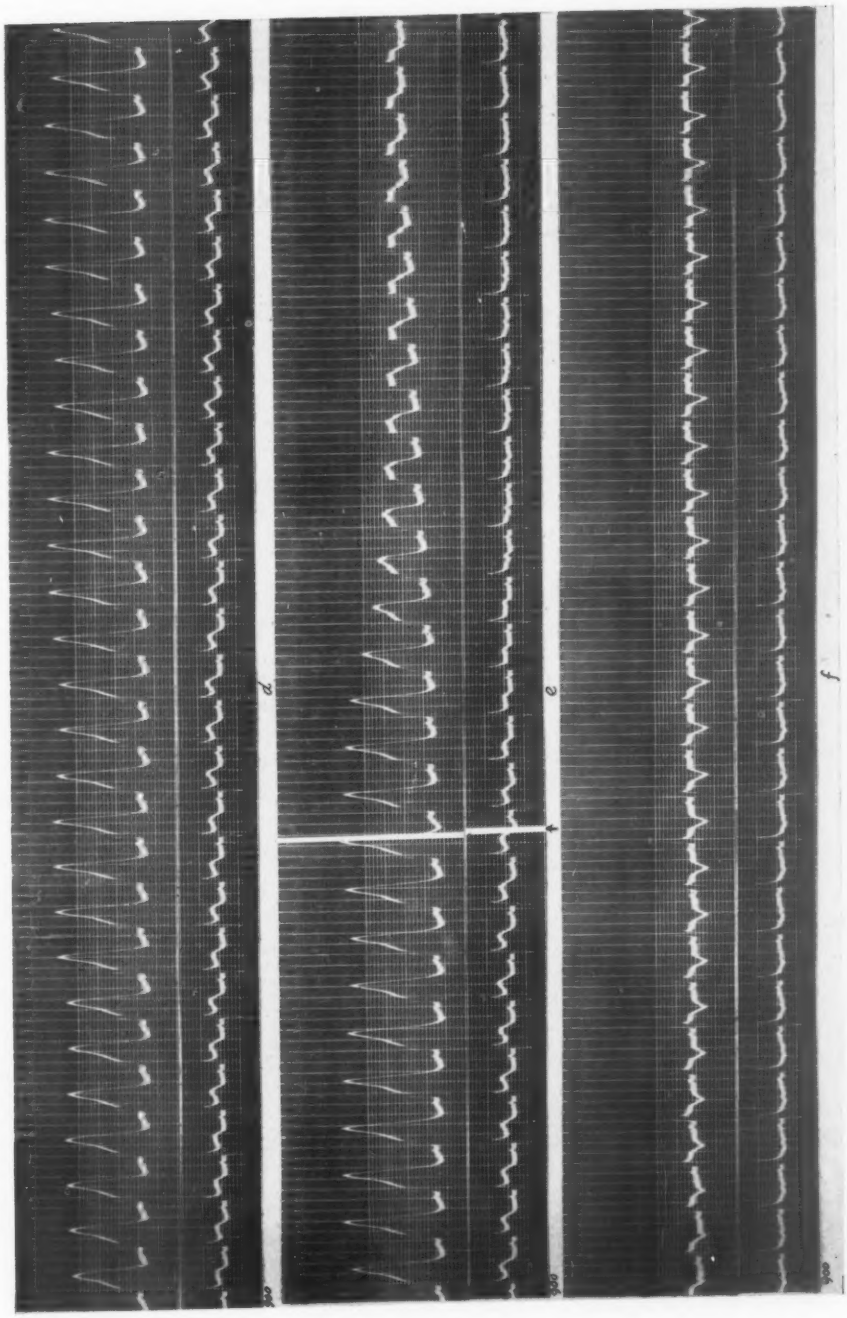

Fig. 7.—See legend of Fig. 5.

coronary artery . . . caused no change in the (extremity-lead) electrocardiogram." We assert that properly placed unipolar leads will invariably show striking electrocardiographic changes of a highly predictable kind when a large coronary artery is suddenly occluded. They state that "change in the position of the heart was not a factor in these electrocardiographic changes." When a unipolar method of leading is employed, in which an exploring electrode is placed on the pericardial sac (or on the heart's surface) superjacent to the tributaries of the occluded artery, it may be safely asserted that the position of the heart is not an influential factor in the kind or magnitude of the electrocardiographic changes associated with the occlusion. On the other hand, we suggest that, when using the extremity leads, the position of the heart may well account for the total absence, the presence, and the direction, singly or in combination, of electrocardiographic changes associated with experimental coronary artery occlusion. Finally, we are able to confirm the major conclusion reached by Wood and Wolferth,[3] namely, that brief coronary artery occlusion is associated with local myocardial changes of slightly longer duration, which are in turn responsible for temporary alterations in the T wave and in the RS-T junction. Our previous [1, 2] and present investigations have attempted to extend the solution of the problem.

It has been shown experimentally,[1] and is now re-emphasized, that the electrocardiographic effects of ischemia precede those of injury, and that this order of appearance is necessarily the same as would occur with myocardial infarction had the latter been permitted to develop by prolonging the occlusion.* Since the duration (ninety seconds, or less) of the occlusion usually produced is about one-twelfth as long as that required to produce minimal pathologic changes,[4] it is clear that the electrical phenomena are entirely independent of demonstrable pathologic changes. Consequently, the ischemia-injury changes, although often associated with infarction in man, are not to be regarded as diagnostic of infarction. In contrast are certain well-recognized, permanent QRS changes which are diagnostic of infarction in man and dog, but which are not observed in the ischemia-injury patterns of brief coronary artery occlusions.

It has been shown elsewhere[2] that the ischemia-injury pattern may be interrupted at any desired stage of its development by terminating the complete occlusion, after which the pattern promptly returns to its control form. It has also been shown[2] that a preparation which yields patterns of the negative T variety may be made to yield patterns of the positive T variety by the administration of theophylline with ethylenediamine. In the present experiments it was demonstrated that the ischemia phase may be produced gradually, in stages, by increasing degrees of subtotal occlusion, and that it can be prolonged in proportion to the duration of subtotal occlusion. After release of

*The same order of appearance may likewise hold for acute pericarditis.

the subtotal occlusion, the T wave gradually reverts to its original form. Finally, it is shown that variable, high-grade occlusion is attended with a variable pattern which moves from the ischemia phase into, and out of, the injury phase, depending upon whether the grade of occlusion is increased or decreased.

The kind of electrocardiographic changes produced by the various kinds of arterial occlusion have occurred repeatedly in a highly predictable manner for an over-all total of twenty dogs, upon each of which an average of four occlusive procedures have been carried out. The evidence, so it seems to us, indicates clearly that a second-to-second relationship exists between the electrical activity (ischemia and injury) produced by the involved myocardium and the quantity (or lack) of arterial blood received; that is, the rate at which the electrical effects change is a rough measure of the rate at which the arterial circulation is impaired or improved for as long a time as the involved muscle is able to respond.

Physiologic Considerations.—Little is to be gained at this time by attempting an analysis of the ischemia-injury pattern. Certain of the broad analytical aspects of comparable electrocardiographic changes in man have been presented elsewhere,[5] and we see no reason why a similar approach is not altogether suitable to homologous electrocardiographic changes in the dog. The diagrams in Fig. 8*b* will serve our present purpose. Let the surface of the paper represent that part of the epicardial surface of the heart which is superjacent to the region of the ventricular wall and is normally irrigated by the dissected artery. At *O* the surface is normal, and complete occlusion has just commenced. At *1* the exploring electrode is shown in the general vicinity of the center of the surface under consideration, in which there has now appeared a small zone of ischemia. Within a second after the onset of occlusion the zone of ischemia will have expanded beyond the electrode tip, and the ischemia phase of the pattern will have commenced (strips *a* and *b*, Fig. 6). In *2* the zone of ischemia is beyond the electrode and the zone of injury is now apparent. In about forty seconds the zone of injury will have reached the electrode. Concurrently, the transition from the ischemia phase into the injury phase takes place (strips *b* and *c*, Fig. 6). At *3* the electrode is shown on the injury zone (about fifty-five seconds after the onset of occlusion), and the injury phase of the pattern is well developed (strip *d*, Fig. 7). Concurrently, the center of the injured zone displays a new kind of activity, possibly because of local release of potassium from the interior of the injured cells.[6] At *4* the (?K) zone involves the electrode, and the "waterfall" T waves are converted gradually into upwardly directed spikes (within sixty seconds after the onset of occlusion). If the occlusion is now suddenly released, the zones rapidly vanish in the reverse order to that in which they appeared (strip *e* and *f*, Fig. 7). If the occlusion is maintained for ten minutes or longer, the initial effect of the (?K) zone gradually vanishes. Presumably, the

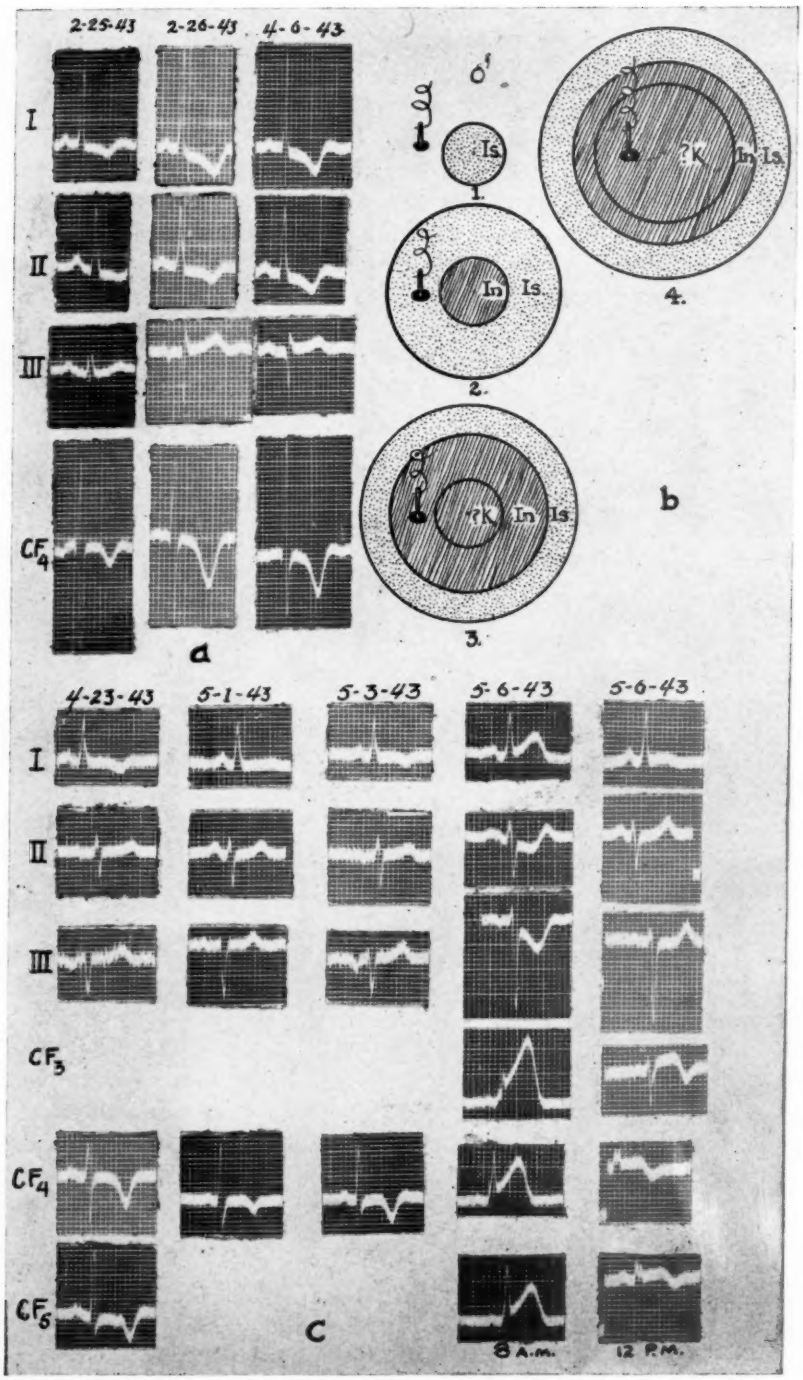

Fig. 8.—*(For legend see opposite page.)*

action of potassium on the injured zone changes, or the injured zone is no longer able to respond in the same way. The effects of more prolonged occlusion are beyond the limits of this communication.

We wish to emphasize that the cardiac muscle of both man[7] and dog[1] ordinarily passes into and out of the injured state through a stage evidenced by primary T-wave changes and called the ischemia phase. It is our present opinion that the injured zone cannot long endure without local death of most of its central region. On the other hand, the ischemia stage is known to exist in man for at least two weeks without the development of detectable microscopic changes.[7]

Clinical Implications.—If infarction can be prevented or minimized at its *impending* stage, the recognition of this stage will be extremely important clinically. At present, the only possible means of recognition in the impending stage is, so far as we know, the proper evaluation of electrocardiograms which display evidence of acute, local, ventricular ischemia.[5, 7] The serial electrocardiograms shown in Fig. 8*a* and 8*c* are two examples of the appearance of acute local ventricular ischemia which later developed into the injury stage and infarction. The latter appeared one day after the discovery of acute local ischemia in one patient (Fig. 8*a*), and within twelve days in the other (Fig. 8*c*).

SUMMARY

1. When the dog's coronary artery is completely occluded for ninety seconds, an essentially unipolar lead, taken with the exploring electrode superjacent to that part of the myocardium which is ordinarily irrigated by the artery, undergoes a highly predictable sequence of changes.

2. The pattern thus obtained has been referred to as the ischemia-injury pattern.[1, 2] The ischemia phase commences almost at once, consists of a primary T-wave change, and lasts from thirty to forty-five seconds.

3. The ischemia phase may be induced gradually, in stages, by subtotal occlusion, the degree of which is increased in a like number of stages. If the subtotal occlusion is promptly ended, the induced T-wave change gradually vanishes.

Fig. 8.—*a*, Three serial electrocardiograms recorded before, during, and after myocardial infarction in a white man, aged 67 years. The curve of Feb. 2, 1943, is interpreted as indicating acute, local ischemia of the ventricular muscle ordinarily irrigated by the left coronary artery. The permanent QRS changes in Lead III of the two subsequent curves indicate "posterior" infarction "at a distance." Cardiac pain was present only at the time of the first recording. The patient had hypertensive arteriosclerotic heart disease. Fever and an increased sedimentation rate developed on Feb. 26, 1943. No leucocytosis or fall of blood pressure occurred.

b, A diagram of the ischemia-injury distribution under development. See text and Figs. 6 and 7.

c, Serial electrocardiograms recorded from a white woman before, during, and after the development of anterolateral infarction. Repeated, fifteen-minute attacks of cardiac pain had occurred for six days prior to Apr. 23, 1943. No further pain occurred until the morning of May 6, 1943, at which time she experienced a most severe four-hour attack. The first three recordings indicate (under the circumstances) acute local ventricular ischemia of varying intensity in the muscle ordinarily irrigated by the left coronary artery. The permanent QRS changes in the last two recordings indicate myocardial infarction. The curve at 8 A.M. shows the (?K) effect. See text.

4. The ischemia phase may be induced almost at once by subtotal occlusion, and its duration is directly proportional to the duration of the subtotal occlusion. A variable, high-grade, subtotal occlusion causes the pattern to evolve from the ischemia phase into and out of the injury phase, depending upon whether the subtotal occlusion is increased or decreased.

5. A brief description of the distribution upon the epicardial surface of the development and the decay of ischemia and injury is offered, and it is pointed out that the analytical approach presented elsewhere for the analogous electrical problem encountered in man[5] appears altogether suitable for the situation encountered in the dog.

6. It is important to know how long local ischemia, associated with only primary T-wave changes, must exist in order to be followed by local myocardial fibrosis. This we have not ascertained, but analogous changes have been known to exist in man for at least two weeks without detectable myocardial change.[7] Serial electrocardiograms recorded from man are presented, in which the ischemia phase gradually evolved into the injury phase and myocardial infarction. It is emphasized that, if a method is developed by which infarction may be prevented or minimized when treated in its impending stage, the recognition of this stage will be of considerable clinical importance. So far as we know, the only means by which the stage of impending myocardial infarction may be recognized is by proper evaluation of electrocardiograms which display evidence of acute, local, ventricular ischemia.[5, 7]

Thanks are given to M. E. Bayley, R.N., and to Dorothy J. York, B.S., for technical assistance. We likewise wish to express our thanks to Dr. James L. Gouaux for permission to use the electrocardiogram in Fig. 8c.

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OBSERVATIONS ON THE HEART SIZE OF NATIVES LIVING AT HIGH ALTITUDES

A. J. KERWIN, M.D.
TORONTO, CANADA

IT HAS been demonstrated by several workers that severe, acute anoxia may cause dilatation of the heart. The effects of chronic anoxia on the heart are, however, by no means clear. There is some experimental evidence to suggest that cardiac hypertrophy may result from prolonged exposure to low concentrations of oxygen. As Van Liere[1] points out, however, there is little or no information in the literature on the heart size of people who live at high altitudes.

During the course of a three-year stay in the Andes, an opportunity was afforded for making observations on this subject. The most useful and accurate information would, of course, have been obtained from autopsies on persons who died from accidents or diseases which are known not to cause cardiac hypertrophy. However, local conditions were not favorable to gathering together a sufficient number of these for study. It was therefore decided to utilize roentgenograms in an attempt to ascertain whether living at a high altitude does cause cardiac enlargement.

MATERIAL AND METHOD

The subjects were normal native Peruvian males of Indian race with a small admixture of white blood in some cases. All had been born at altitudes varying from 10,000 to 15,000 feet, and, with a few exceptions, had lived all their lives at these altitudes. Some had made trips to lower levels or even to the seacoast, but usually not for more than a few months. These men were either applying for work in the smelter or mines or were anxious to leave the company employ.

Their ages ranged from 17 to 66 years. It was recognized that in some cases his exact age was unknown to the man himself, but it is unlikely that the individual discrepancy amounted to more than a couple of years, and, in a large series, the errors would tend to cancel out.

In each case the height was measured in centimeters and the weight in kilograms. An attempt was made to obtain a history of previous illnesses, although the value of the answers was frequently doubtful. A complete physical examination was done, including measurement of the blood pressure and testing of the urine for albumin.

Those who were suffering from detectable cardiac disease were excluded from the study. Electrocardiograms were not taken routinely, but, when an abnormality was found, the case was not included. Cases of hypertension (with a pressure of more than 140/90), thyroid disease, albuminuria, and tuberculosis were eliminated, as were cases of suspected illness in which a definite diagnosis could not be made in the time

This work was carried out in Oroya, Peru (altitude 12,200 feet), during the years 1937 to 1940. Analysis and publication of the data have been delayed because of the war.

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available. Special care was taken to rule out pulmonary disease, particularly pneumoconiosis. Among the older subjects it was, of course, not possible to exclude all cases of asymptomatic coronary disease, but it is not likely that any considerable number of these was used.

The roentgenograms were taken at a distance of 6 feet, and the exposure time was $\frac{1}{20}$ second. Exposures were made in the postero-anterior direction at the end of normal inspiration. Consideration was given to the use of lateral views in an attempt to estimate the heart volume by means of a formula such as the Rohrer-Kahlstorf, but the defects of any such formula seemed too great to justify the expense and time involved.

The transverse, long, and broad diameters were measured in the usual way. The frontal area was estimated from the long and broad diameters by means of the nomogram of Ungerleider and Gubner.[2] The estimate of the effect of altitude on heart size was based on the transverse diameter and the frontal area. The imperfections of these two measurements, particularly in borderline cases of enlargement, are too well known to require discussion. Criticism of their shortcomings is, however, applicable chiefly in the individual case, particularly when only one set of figures is available. The objections are much less applicable to a large number of cases such as this series.

The ideal method of ascertaining the effect of high altitude on heart size would have been to compare these data with those derived from normal Peruvian Indian inhabitants at sea level. Since figures for the latter were not available, it was decided to compare the measurements with the normal standards for white persons living near sea level, recently published by Ungerleider and Clark[3] and Ungerleider and Gubner.[2] The possible objections to this procedure will be discussed later.

From the nomograms of Ungerleider and Gubner,[2] the predicted "normal" transverse diameters and frontal areas were ascertained for these natives on the basis of their heights and weights, and these were compared with the actual observations. As an indication of deviation from the standards it was decided to use the percentage changes above or below the "normal" predictions as the raw data, rather than the actual differences. These percentage changes were calculated to the nearest whole figure, for it was felt that the use of decimal places was not justified. The information thus obtained was subjected to statistical analysis.

RESULTS

In all, 273 persons were regarded as suitable for analysis. This sample of the population was unselected with the exceptions noted above, i.e., the exclusion of those suffering from diagnosable disease.

The average height of these subjects was 156.26 cm., and the average weight, 55.63 kg.

Transverse Diameter.—The percentage variations from the predicted "normals" were divided into ten groups of 5 per cent each, ranging from –10 per cent to +35 per cent. The number and percentage of the total are shown in Table I.

A histogram showing the distribution of these cases is presented in Fig. 1.

Fig. 2 shows the frequency distribution curve of these same cases, together with the distribution curve of the 1,460 white persons who

formed the basic data of Ungerleider and Clark's tables.[3] For more accurate comparison the grouping in this series was abandoned, and, to provide a curve of comparable size, the number of cases in each percentage was multiplied by approximately 5.4. Only the smoothed curve of Ungerleider and Clark is shown; the actual numbers of my series are plotted, and an approximate curve is drawn through these. The table and figures show that the transverse cardiac diameters of these natives were definitely greater than the normal standards for white males. The average percentage change in transverse diameter (T. D.) for all cases was +11.5 per cent, with a standard deviation of 7.1; the standard error of the latter was 0.30.

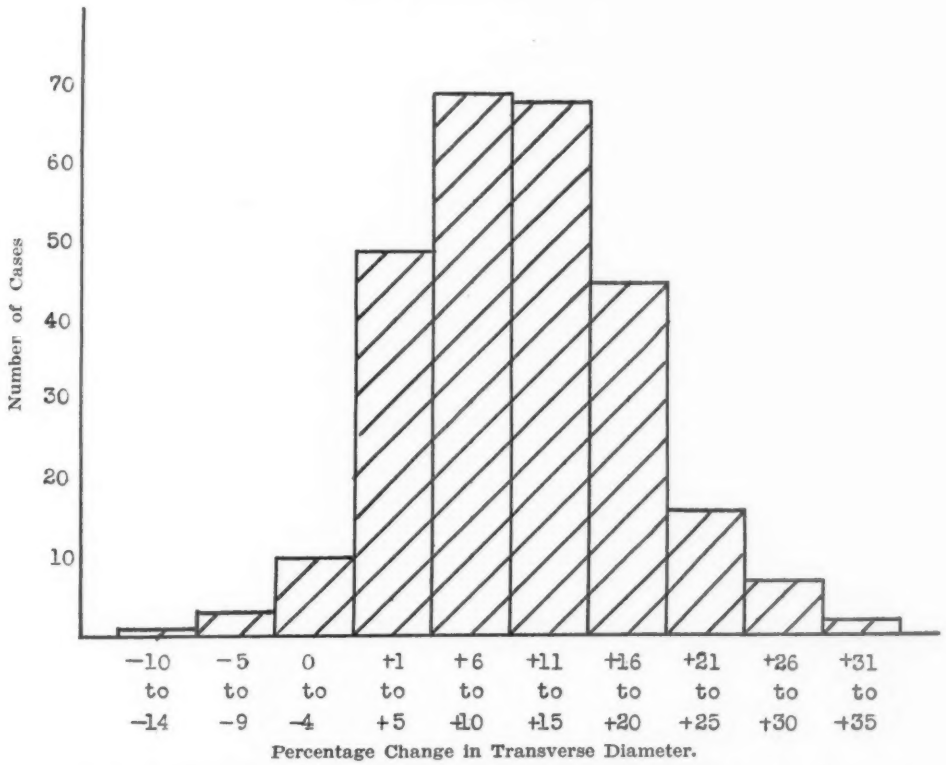

Fig. 1.—Histogram showing the frequency distribution of cases for varying percentage changes in transverse diameter.

TABLE I

PERCENTAGE CHANGE IN TRANSVERSE DIAMETER	−10 TO −14	−5 TO −9	0 TO −4	+1 TO +5	+ 6 TO +10	+11 TO +15	+16 TO +20	+21 TO +25	+26 TO +30	+31 TO +35
Number of cases	1	3	10	49	69	68	45	16	10	2
Percentage of total	0.37	1.1	3.6	18.0	25.3	24.9	16.5	5.9	3.6	0.73

Comparison of the frequency distribution curves in Fig. 2 suggests that this is at least as valid a sample of the population as is that of Ungerleider and Clark.[3] It is obvious that the range of measurements is significantly shifted to the right, and that the values are definitely higher.

Table II shows an analysis of the influence of age on the percentage change in transverse diameter. If one uses an increase of 10 per cent, or more, over the predicted "normal" as an indication of "enlargement," one can then ascertain the number in each age group who have "enlargment" according to the standards for white males. The average percentage change in transverse diameter for each age group is also shown.

TABLE II

AGE GROUPS	UP TO 19 YR.	20 TO 24 YR.	25 TO 29 YR.	30 TO 34 YR.	35 TO 39 YR.	40 TO 44 YR.	45 YR. AND OVER
Number of cases	25	43	81	52	35	20	17
Number with increase in T.D. of +10 per cent or more	6	20	44	27	26	13	15
Percentage with increase in T.D. of +10 per cent or more	24	47	53	55	74	65	88
Average percentage change in T.D. in all cases	+6.4	+11.3	+10.7	+11.1	+13.9	+12.0	+18.2

The percentage of those with "enlargement" in each group appears at a glance to show a rise with advancing age. On applying the chi square test to these figures, one finds that p is just greater than 0.05. This is about the value of p which is usually taken to be of significance; such a series of figures would be encountered by chance only about once in twenty samples. This point will be discussed later in connection with the results on frontal areas. Except at the extremes of the age groups, there is an insignificant variation in the average percentage increase in transverse diameter. The chi square test gives a value of $p = 0.37$, so that such a set of results could easily arise by chance.

Table III shows the average percentage increase in the transverse diameter for the various predicted "normals," which have been grouped into seven classes. In the five classes containing sufficient numbers for comparison, there is no significant variation in the average percentage change.

TABLE III

PREDICTED "NORMAL" T.D.	10.5 TO 10.9	11.0 TO 11.4	11.5 TO 11.9	12.0 TO 12.4	12.5 TO 12.9	13.0 TO 13.4	13.5 TO 13.9
Number of cases	2	29	103	89	41	8	1
Average percentage change	+24.5	+10.6	+10.0	+11.7	+11.5	+11.1	+2.0

Likewise, as seen in Table IV, the subject's surface area had no influence on the average percentage change in transverse diameter.

The data on the broad and long diameters were not analyzed separately, but the average broad diameter (10.52 cm.) was 20.9 per cent less than the average transverse (13.30 cm.). The average long diameter (14.19 cm.) was 6.7 per cent greater than the average transverse diameter.

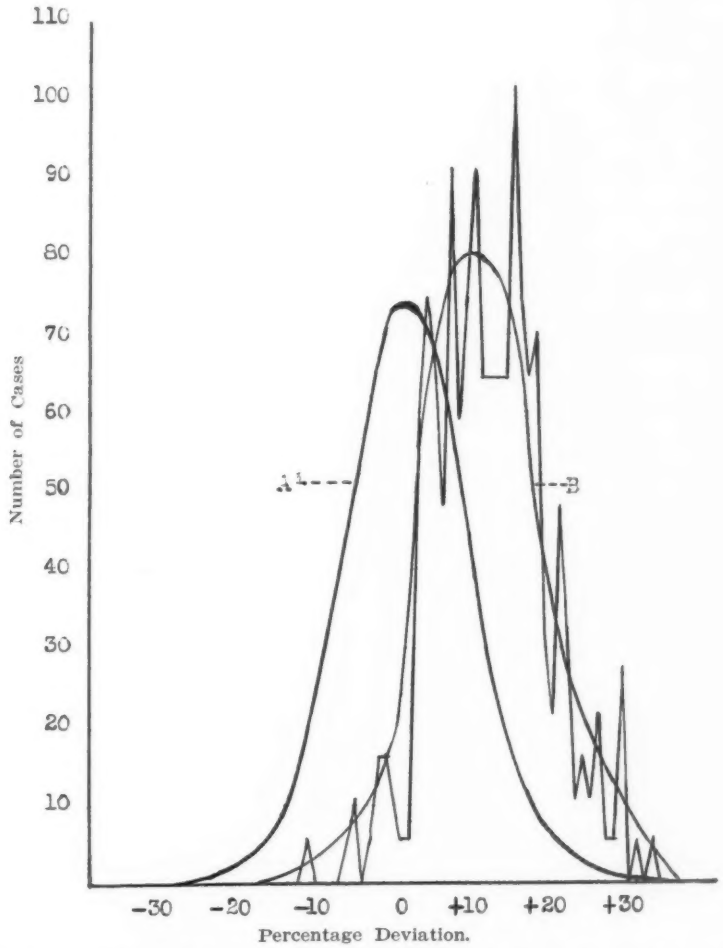

Fig. 2.—*A*, Smoothed curve of Ungerleider and Gubner's[2] 1,460 cases, forming the normal standards (the plotting of the original data is omitted to avoid confusion in the diagram). *B*, Curve of the data in this series of 273 cases, multiplied by 5.4 to provide a diagram of comparable size. A smoothed curve derived from this is also shown.

Frontal Area.—The percentage changes in frontal area (F. A.) were divided for convenience into groups of 8 per cent each, ranging from below –16 per cent to over +44 per cent. Table V shows the numbers and percentage of the total in each group. Fig. 3 shows the distribution of these cases.

TABLE IV

SURFACE AREA IN SQ. M.	UP TO 1.40	1.41 TO 1.45	1.46 TO 1.50	1.51 TO 1.55	1.56 TO 1.60	1.61 TO 1.65	1.66 TO 1.70	1.71 AND OVER
Number of cases	17	25	57	61	57	28	18	10
Average percentage change in T.D.	+13.8	+13.4	+9.9	+11.8	+11.1	+10.7	+11.1	+9.7

TABLE V

PERCENTAGE CHANGE IN FRONTAL AREA	UP TO -16	-8 TO -15	0 TO -7	+1 TO +8	+9 TO +16	+17 TO +24	+25 TO +32	+33 TO +40	+41 TO +48	+49 AND OVER
Number of cases	1	9	24	50	61	58	37	15	9	9
Percentage of total	0.37	3.3	8.8	18.3	22.3	21.2	13.5	5.5	3.3	3.3

Here, as in the case of the transverse diameter, there is a definite increase in the frontal area over the normal for sea level inhabitants. No frequency distribution curve on frontal areas of normal whites was available for comparison with these data. The average percentage change in frontal area was +16.3 per cent, with a rather large standard deviation of 14.4; the standard error of the latter was 0.61.

Table VI shows the influence of age on the percentage variations in frontal area; this is analyzed in a fashion similar to that of Table II for transverse diameters. Inspection does not suggest that there is a significantly increasing "enlargement" with advancing age within the limits of the groups studied. This is borne out by the chi square test, which gives a p of 0.60.

TABLE VI

AGE GROUPS	UP TO 19 YR.	20 TO 24 YR.	25 TO 29 YR.	30 TO 34 YR.	35 TO 39 YR.	40 TO 44 YR.	45 YR. AND OVER
Number of cases	25	43	81	52	35	20	17
Number with increase in F. A. of +10 per cent or more	9	32	52	34	24	12	13
Percentage with increase in F. A. of +10 per cent or more	36	74	65	65	69	60	76
Average percentage change in F. A. in all cases	+6.8	+16.0	+17.0	+18.2	+18.5	+18.4	+14.9

TABLE VII

PREDICTED "NORMAL" F. A.	UP TO 87	88 TO 90	91 TO 93	94 TO 96	97 TO 99	100 TO 102	103 TO 105	106 TO 108	109 TO 111	112 AND OVER
Number of cases	5	14	16	30	56	43	48	28	21	12
Average percentage change	+31.6	+25.0	+22.5	+19.8	+13.8	+16.7	+14.1	+12.1	+11.7	+10.5

In Table VII the predicted frontal areas have been divided into ten groups, and for each the number of cases is shown, along with the average percentage change. There is an obvious downward trend in the percentage variation, with increasingly larger predicted "normal" frontal areas. This impression is supported by the chi square test, in which p is less than 0.01; this is strong evidence that this result is not due to sampling error.

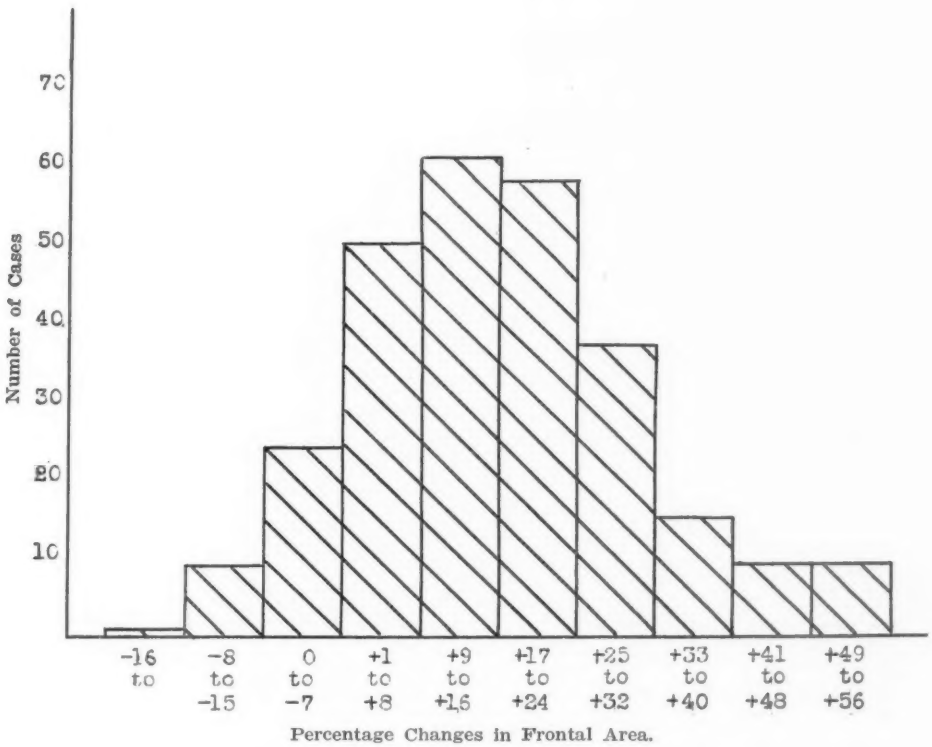

Fig. 3.—Histogram showing the frequency distribution of cases according to varying percentage changes in frontal area.

Table VIII shows the variation in percentage changes in frontal area for different surface areas. The chi square test reveals a p of 0.7, which suggests that the variations are a matter of chance.

TABLE VIII

SURFACE AREA IN SQ. M.	UP TO 1.40	1.41 TO 1.45	1.46 TO 1.50	1.51 TO 1.55	1.56 TO 1.60	1.61 TO 1.65	1.66 TO 1.70	1.71 AND OVER
Number of cases	17	25	57	61	57	28	18	10
Average percentage change in F. A.	+20.4	+23.2	+15.5	+15.8	+15.1	+13.3	+16.6	+14.8

DISCUSSION

As previously pointed out, a comparison of the heart sizes of high altitude inhabitants with those of a population similar in every respect, but living near sea level, would be a desirable method of ascertaining the effect of chronic anoxia on the heart. However, under the circumstances, the measurements obtained had to be compared with those of normal white males. This procedure is open to the obvious objection that the two groups differ in more respects than merely the altitude at which they live. They differ in race, amount and type of work and exercise, nutritional status, and in other respects. It is not known exactly what influence these factors may have, but it is unlikely that many of them have a significant effect on cardiac size. The most serious error may well lie in our inability to take purely racial variations into account.

Anthropometric studies on Indians have concerned themselves largely with external and skeletal measurements, and I am not aware of any data on the sizes and weights of internal organs. It appears probable that there is little variation other than the individual differences which are common to all races. That the Peruvian Indians used in this study are among the smaller Indian tribes of America can be seen from a comparison of their average height with the tables of average statures for various tribes given by Steggerda.[4] In this respect they are similar to the tribes of Southern Mexico and Central America, such as the Mayas. It is worthy of note that the ranges of stature among Indian tribes are comparable to those of various white groups.[4] One may, therefore, suggest that individual height and weight differences,* which are here taken into account, are of much greater importance in determining heart size than are racial differences. This view is supported by Comeau and White,[5] who state: "The conclusion is reached that heart size in normal individuals is dependent principally on body build, and that genetic, racial, and environmental factors are usually important chiefly as they affect body structure."

The observations reported here show that the heart size, as measured by the transverse diameter and frontal area, is significantly greater among native residents of high altitudes than among white persons living near sea level. One cannot dogmatically assert, for the reasons given, that chronic anoxia is the causative factor, but it seems to be a reasonable explanation.

The following questions logically arise: Is this "enlargement" an inherited and permanent characteristic, or does it begin in infancy or childhood? Does it increase progressively throughout life, or even reach a certain degree and then cease? The figures available do not provide a definite answer because of lack of data on younger subjects.

*Ungerleider and Clark[3] concluded that, although short men have an average transverse diameter of the heart which is 1 or 2 mm. greater than that predicted in their tables, the difference was so slight as to make any further correction for height unnecessary.

It is to be noted that both the transverse diameter and frontal area show a smaller average increasein the subjects who were 17 to 19 years old than in subjects at other ages. Whether or not this is significant cannot be decided at present. Application of the chi square test to both sets of figures reveals that this result could well have been a sampling error. If one studies the percentage of cases of "enlargement" at various ages, the chi square test on the figures for transverse diameter is borderline, i.e., we are reaching the point at which chance is unlikely to be the cause. However, the results with frontal areas do not corroborate this. One must conclude that certain evidence of progressive "enlargement" between the ages of 20 and 45 years is lacking.

As might be expected, the subject's surface area had no influence on the changes in heart measurements.

Variations in the predicted "normal" transverse diameter had no effect on the percentage changes which occurred. However, in the case of frontal areas, there was a progressive fall in the average percentage change for increasingly large predicted frontal areas (see Table VII). This result, as indicated above, can scarcely be due to chance, but the explanation for it is obscure.

The results of experimental studies on the effect of low oxygen concentrations on the heart are of some interest. Takeuchi,[6] among others, was able to produce definite cardiac dilatation in cats by having them inhale mixtures of nitrogen and air. It was his impression that a large proportion of the change occurred in the lower degrees of anoxemia. At a blood oxygen saturation of 85 per cent, the heart was much dilated. Hilton and Eichholtz[7] showed that the state of contraction of the coronary vessels was proportional to the oxygen saturation of the blood; a fall of oxyhemoglobin saturation below 20 per cent caused maximal dilatation. While confirming, in general, these results in respect to coronary flow, Gremels and Starling[8] found that the degree of oxygen saturation had no influence on heart volume until it fell to 40 per cent; dilatation then occurred and progressed as the saturation fell to 8.5 per cent. They concluded that, under anoxemia, the heart takes up oxygen by an augmented coronary flow and by an increased coefficient of utilization. In more prolonged experiments, Van Liere[9] demonstrated that, when guinea pigs were exposed to simulated altitudes of 14,000 to 18,000 feet for periods up to 105 days, there was an average increase in the heart weight/body weight ratio of 55.8 per cent.

It is apparent, of course, that the time element is relatively short, and that conclusions drawn from such experiments may not necessarily be applicable to human beings who have been exposed to anoxia for years or even generations.

Results similar to those in animals have been obtained in short term experiments on human beings. Whitney[10] reported that five out of ten men in a low pressure chamber at varying altitudes above 14,000 feet developed cardiac dilatation; in each case, severe symptoms of acute alti-

tude sickness ensued. In carefully controlled experiments, however, Le Wald and Turrell[11] produced no significant change under acute anoxia.

Barcroft and others[12] during the Peru expedition could find no consistent changes in the cardiac diameters of several of the expedition members; in fact, in two cases the heart appeared to be smaller. The observations were too few and not sufficiently controlled for any conclusions to be drawn; no data on high altitude residents were collected. Talbott and Dill[13] reported studies on healthy persons living at 17,500 feet. Roentgenographic facilities were not available, apparently, but in each case it was noted that the heart was not enlarged to percussion. No inferences can be drawn from this for several reasons. Percussion is very likely to mislead, particularly in cases of emphysema, and this was present in five of the six cases studied. Moreover, all of these men had been born in the lowlands of Chile or Bolivia, and had been resident in high altitudes for only two to fourteen years. In our present state of knowledge, one cannot regard them in the strictest sense of the term as "permanent inhabitants," as do Talbott and Dill.

It is perhaps not always remembered that hypertrophy in itself does not contribute the major portion to even a moderate enlargement of the cardiac silhouette. For example, an increase of 1 cm. in the thickness of the left ventricular wall, which, from the pathologist's viewpoint, is respectable, would not necessarily widen the transverse diameter a significant amount. It is therefore reasonable to assume that dilatation is always present when there is enlargement of the heart. In the absence of autopsy data, it is not possible to say how much of the "enlargement" in these cases was due to hypertrophy and how much to dilatation.

The mechanism and significance of this "enlargement" are as yet uncertain. Hill[14] expressed the opinion that cardiac hypertrophy may be an "important means of acclimatization" to high altitudes. Probably the fundamental cause is oxygen lack, and it appears likely that this operates directly on the cardiac muscle, which, at the altitudes in question, is exposed to arterial oxygen saturations of about 80 to 87 per cent. In spite of the adaptive mechanisms by which the cardiac fiber acquires its necessary supply of oxygen, such as a greater amount of circulating hemoglobin, dilatation of the coronary vessels, an increase in the coefficient of oxygen utilization, and perhaps an increase in cardiac muscle hemoglobin (Hurtado, et al.[15]), it is possible that, over long periods of time, these measures are not sufficient. A permanent increase in the length of the cardiac fiber may be necessary to liberate the required energy, and, in time, this would result in hypertrophy. Other factors, such as acceleration of the development of coronary sclerosis, may play a part.

It has been suggested that the increased viscosity of the blood places an added strain on the heart,[16] and might therefore lead to enlargement.

There are at least two serious objections to this theory. Although the blood viscosity of high altitude residents is much increased, the increase is due entirely to the augmented number of erythrocytes; the viscosity of the serum is unchanged. As measured in vitro by an instrument such as the Hess viscosimeter, the viscosity increment is much greater than in vivo, for the flow of the more numerous erythrocytes, which is responsible for the increase, is largely axial in the arterioles (Dill[17]). Moreover, increased viscosity in the systemic circulation could operate only by raising the peripheral resistance and thereby elevating the blood pressure. Hypertension is not unusually frequent among inhabitants of high places.

It is interesting to note that persons suffering from chronic mountain sickness, or Monge's disease, nearly always have abnormally large hearts. This was true in five out of seven of Hurtado's[18] cases. In this disease much emphasis has been placed on the hematologic changes, which, in some respects, resemble those of polycythemia vera. It may be that insufficient attention has been paid to the cardiovascular changes which contribute to the disability and may play an important part in the periodic exacerbations of the disease from which these people suffer.

SUMMARY

A study was made of the cardiac measurements, as ascertained roentgenographically, of 273 normal native Peruvian male residents of high altitudes. The data obtained were compared with the normal predicted values for white persons living near sea level.

As judged by the transverse diameter and frontal area, the size of the cardiac silhouette was definitely greater in these people than in normal white inhabitants of low altitudes. The average increase in transverse diameter was 11.5 per cent, and, in frontal area, 16.3 per cent. In the age groups studied, no progressive enlargement with increasing age was evident.

The possible mechanism and significance of this "enlargement" are discussed. It is suggested that this may be one of a variety of adaptive changes which occur with prolonged exposure to low concentrations of oxygen.

I am indebted to Dr. H. L. Crane, chief surgeon of the Cerro de Pasco Copper Corporation, Oroya, Peru, for permission to use these data.

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MYOCARDIAL INFARCTION INDICATED BY ANGINA PECTORIS OF EFFORT OR BY BRIEF ATTACKS OF ANGINA OF REST, WITH REMARKS ON PREMONITORY PAIN

WILLIAM DRESSLER, M.D.
NEW YORK, N. Y.

WHEN the blood supply to the heart muscle becomes inadequate relative to its needs, angina pectoris develops in susceptible persons. Angina of effort ("Heberden's angina") is thought, as a rule, to be associated with a reversible nutritional disturbance. As soon as the demands on the heart are decreased, the anginal pain subsides, and no structural damage to the myocardium results. When, however, relative ischemia is severe and protracted, myocardial infarction takes place, even in the absence of complete occlusion of coronary branches. In typical cases, myocardial infarction is indicated by anginal distress more severe and protracted than that which usually accompanies reversible damage of the myocardium. The pain lasts one hour, or several hours, or even days, and is not relieved by rest or nitroglycerin. It may be associated with profuse perspiration, collapse, nausea, and vomiting. It is followed by fever, leucocytosis, a fall in blood pressure, rapid sedimentation of the erythrocytes, a pericardial friction rub, and progressive electrocardiographic changes.

The outstanding symptom of myocardial infarction that usually calls for medical care is pain of unusual severity and duration. However, there are atypical cases in which the symptom of pain is less characteristic. Atypical features are said to be present in 40 per cent of the cases of myocardial infarction.[1] Anginal pain may be entirely absent, and myocardial infarction be suggested only by the sudden development of congestive heart failure, pulmonary edema, or severe fatigue.[2-7] Painless attacks are infrequent, however. Thorough questioning elicits the fact that there was some kind of anginal pain in the overwhelming majority of cases.[8, 9] A subacute course of myocardial infarction has also been described, without startling manifestations in the beginning, and with vague symptoms and delayed electrocardiographic changes.[10]

In the great majority of atypical cases, myocardial infarction is associated with mild anginal pain or with distress of short duration.[1, 2, 4, 6, 11] Herrick,[4, 9] in his early reports on the clinical manifestations of myocardial infarction, has mentioned the occurrence of mild attacks which, in his opinion, were more frequent and of greater im-

From the Cardiac Clinics of the Israel Zion Hospital and the Brooklyn Hospital in Brooklyn, N. Y.
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portance than was generally realized. They are deceptive and treacherous, often ignored by patients, and neglected by physicians. The victims frequently overstrain their hearts and succumb to ventricular fibrillation. Herrick stressed the necessity of studying "in what way may the cases be recognized more definitely" and "what are the minimum signs and symptoms" of myocardial infarction.[12] We are still far from having fully answered these questions.

In a study undertaken during the last two years, we have investigated the features of atypical cases of myocardial infarction with special reference to the anginal manifestations. The occurrence, the character and duration, and the precipitating causes of anginal pain were ascertained by painstaking questioning. Each patient was questioned by myself and another physician. Such patients as gave a vague history, or were not intelligent enough to answer questions satisfactorily, were excluded from this study. The present report includes sixteen cases in which clinical and laboratory evidence suggested myocardial infarction, although the anginal manifestations were atypical. No history of a severe, protracted anginal pain of the classical type was obtained. In nine cases anginal pain associated with effort was the main symptom, and there was no angina of rest. In seven other instances the occurrence of myocardial infarction was indicated by brief anginal attacks at rest, lasting but a few minutes, and sometimes even relieved by nitroglycerin. The significant features of the atypical attacks are illustrated in the following case reports.

CASE REPORTS

CASE 1.—J. B., a white man, aged 64 years, in February, 1932, after pushing his car, suffered an attack of severe precordial pain which lasted several hours. Myocardial infarction had then been diagnosed in the Cardiac Clinic. Recovery from this attack was complete, and the patient was able to walk as many as fifty blocks without experiencing discomfort.

Early in March, 1941, while walking on the street, the patient felt a sharp, terrific pain substernally and radiating to the jaw. When he stopped walking the pain subsided. Similar attacks occurred on the following days. Walking a distance of two or three blocks caused pain in the chest. Two electrocardiograms, taken March 11 and 18, 1941 (Fig. 1, *A* and *B*), failed to reveal significant changes; but the sedimentation rate (Westergren) was 68 mm. on March 12, 1941, and the leucocyte count was 11,600. The condition improved somewhat in the second half of March; the patient could walk a distance of six or seven blocks without experiencing pain, and the sedimentation rate fell to 36 mm.

In April, 1941, the anginal attacks again became more severe; they occurred even at rest, often at night, and lasted from ten to twenty minutes. They were promptly relieved by nitroglycerin. The patient had 10 to 12 anginal attacks of short duration within twenty-four hours. An electrocardiogram taken April 24, 1941 (Fig. 1, *C*), showed flattening of T_1, together with an increase in the voltage of T_3. These signs

were interpreted as indicative of myocardial infarction.[13-15] Also, inversion of the T wave had developed in the precordial lead. Although strict bed rest was instituted, the patient suffered, on April 30, 1941, a severe attack of protracted anginal pain which required the administration of morphine. On the following day a pericardial friction rub was heard. An electrocardiogram taken May 1, 1941 (Fig. 1, *D*), showed inversion of T_1 and low voltage of QRS in the standard leads. R_4 had disappeared, and the inversion of T_4 was more pronounced. Another violent anginal attack occurred May 10, 1941; it was followed by pulmonary edema, and the patient grew rapidly worse. An electrocardiogram taken May 12, 1941 (Fig. 1, *E*), showed a downwardly directed main deflection and elevation of S-T in Lead I; there were also a high take-off of S-T and elevation of T in Lead IV. The patient died May 22, 1941.

Post-mortem examination revealed marked arteriosclerotic narrowing of the coronary arteries. The right coronary artery was almost completely occluded by an old thrombus. The apical region of the left

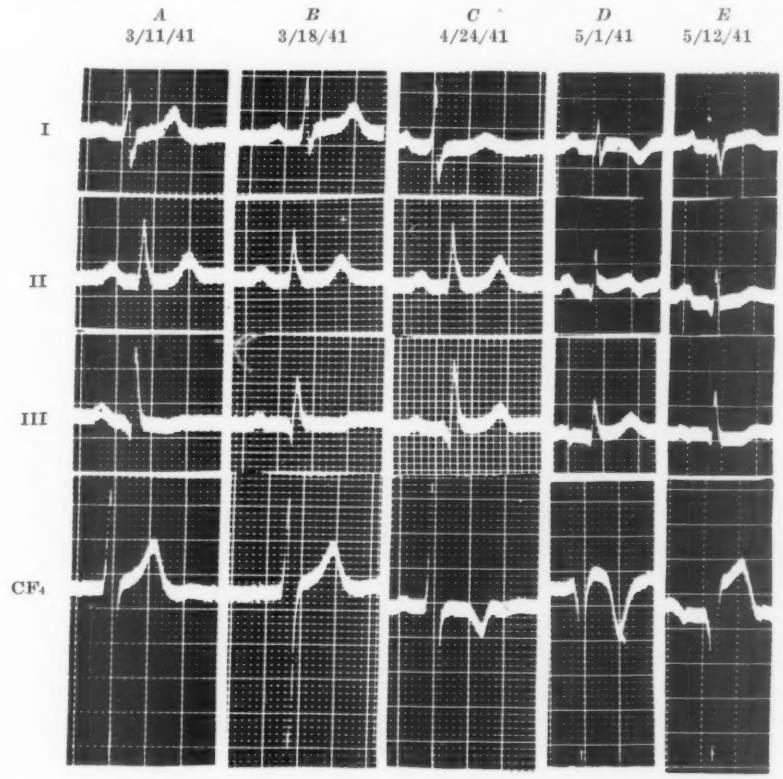

Fig. 1.—Case 1. Severe angina of effort since early in March, 1941. Tracings *A* and *B*, taken March 11 and 18, 1941, showed no significant changes. Numerous brief anginal attacks on rest occurred in April, 1941. Tracing *C*, taken April 24, 1941, showed flattening of T_1, with increase in voltage of T_2: also, inversion of T_4. A new, severe, anginal attack, followed by pericardial friction rub, occurred April 30, 1941. Tracing *D*, taken the next day, showed low voltage of QRS in the standard leads and inversion of T_1. R_4 had disappeared, and inversion of T_4 was even more pronounced. Another severe anginal attack took place May 10, 1941. Tracing *E*, taken after two days, showed a downward main deflection in Lead I. S-T had become slightly elevated and fused with the diphasic T wave in Lead I. The S-T segment was depressed in Lead III. Lead IV showed, besides absence of R, elevation of S-T; T_4 had become upright.

ventricle was thinned, and its muscle replaced by fibrous tissue. In addition, there were large areas of yellowish discoloration, with hemorrhages, indicating recent infarction, in the lateral wall of the left ventricle and in the interventricular septum. Whitish streaks of fibrosis were also visible in the posterior wall of the left ventricle.

Severe angina pectoris of effort and, later, short anginal attacks of rest, relieved by nitroglycerin, preceded the typical attack of myocardial infarction. The initial attacks would readily fit into the designation "premonitory pain," were it not for the increased leucocyte count and sedimentation rate which accompanied the phase of angina of effort, and the electrocardiographic changes during the period of brief anginal attacks of rest. Thus, we are led to believe that the "premonitory pain" indicated the onset of myocardial necrosis in a period of progressive coronary insufficiency which finally culminated in extensive myocardial infarction.

CASE 2.—E. S. was a white woman, aged 52 years. Her father and uncle had died from heart disease in their early fifties. The cardiac complaints of the patient started suddenly on Aug. 1, 1941. While walking, she felt a violent substernal pain which radiated to the right half of the chest and right shoulder and arm. Thereafter she was unable to walk, even slowly, more than one-half block without experiencing pain in the chest. When she rested the pain promptly subsided. No attacks of pain occurred during rest. The patient was first examined in December, 1941. There were no abnormal physical signs. The blood pressure was normal. The sedimentation rate, tested twice during December, 1941, was elevated (55 and 40 mm., respectively). The blood Wassermann reaction was negative. An electrocardiogram taken Dec. 11, 1941 (Fig. 2, *A*), showed a shallow, inverted T_1, with upright T_2 and T_3. T_4 was sharply inverted. On Dec. 31, 1941, the electrocardiographic changes had partly disappeared (Fig. 2, *B*). T_1 was upright, but of low voltage, and the inversion of T_4 was less pronounced. After four weeks' rest in bed the condition of the patient had improved little. Walking only one block caused pain and forced the patient to rest. After taking nitroglycerin the patient was able to walk two or three blocks before pain developed.

This patient suffered from angina of effort, and had never experienced pain at rest. The increased sedimentation rate and significant electrocardiographic changes pointed to myocardial infarction. The anginal syndrome which signalized myocardial infarction had two significant features. It had started suddenly; in fact, the patient remembered after five months the exact date when she first experienced pain on effort. And the complaints were of marked severity; pain in the chest was produced by walking a distance of only one-half block.

CASE 3.—M. S. was a white man, aged 66 years. When the patient was first seen in the Cardiac Clinic, on Feb. 20, 1942, he gave a history of anginal complaints of four years' duration. A burning pain was felt substernally when the patient walked fast on level ground, or slowly

uphill; the pain subsided promptly when effort was discontinued. There had never been angina of rest. An electrocardiogram taken Feb. 20, 1942, showed deep Q waves and inversion of T in Leads II and III.

This patient presented a history of angina of effort of four years' duration; he had never experienced anginal pain during rest. The electrocardiogram showed changes that are usually associated with posterior wall infarction.

CASE 10.—H. J. was a white man, aged 52 years. The fact that he had hypertension had been discovered ten years before. Beginning early in 1941, the patient experienced substernal pressure when he walked in the morning. In November, 1941, a subtotal gastrectomy was performed because of gastric ulcer. Two weeks after the operation, while the patient was resting in bed, he suffered an attack of substernal

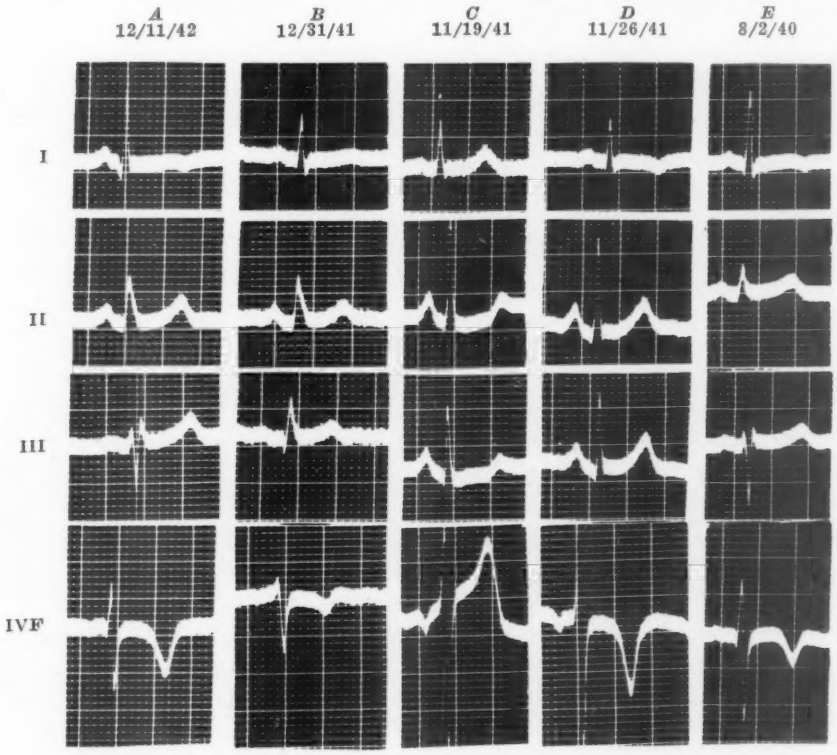

Fig. 2.—Case 2. Severe angina of effort had developed suddenly on Aug. 1, 1941. No angina of rest. Tracing *A*, taken on Dec. 11, 1941, showed a shallow, inverted T_1, with upright T_2 and T_3. T_4 was sharply inverted. *B*, After three weeks, T_1 had become upright, but was still of low voltage, and the inverted T_4 had decreased in voltage.

Case 10. Angina of effort since early in 1941. Gastrectomy was performed Nov. 4, 1941. An attack of substernal pressure of ten minutes' duration occurred Nov. 19, 1941; it was followed by similar attacks on the next few days. Tracing *C* was taken on the day of the first anginal attack. It showed distinct depression of S-T in Leads II and III (without elevation of S-T in Lead I). There was elevation of S-T in Lead IV, and T_4 was upright and of marked amplitude. Tracing *D*, taken seven days later, showed inversion of T_1 and sharp inversion of T_4.

Case 11. Angina pectoris of effort for four months. Two attacks of angina of rest, lasting about fifteen minutes, had occurred six weeks prior to examination. Tracing *E*, taken Aug. 2, 1940, showed convex S-T and late inversion of T in Lead I. There was also sharp inversion of T_4.

pressure with radiation to both arms. The pain was associated with profuse perspiration and lasted ten minutes. Similar attacks followed in the next few days; none lasted longer than ten minutes. Marked weakness developed after these attacks. The temperature rose to 101.4° F. on the day after the first anginal attack. The sedimentation rate, which had been 13 mm. (Westergren) prior to the anginal seizures, increased to 31 mm. on the ninth day, and to 37 mm. on the thirteenth day, after the onset of the anginal attacks. Electrocardiographic examination (Fig. 2, *C* and *D*) revealed progressive changes resulting in inversion of the T waves in Leads I and IV.

This patient, who had suffered from angina of effort for a year, experienced, after an abdominal operation, a few brief anginal attacks while he was at rest, none of which lasted more than ten minutes. The subsequent rise in temperature, increased sedimentation rate, and electrocardiographic changes pointed to myocardial infarction.

CASE 11.—W. L. was a white man, aged 48 years. When he was first seen in the Cardiac Clinic, Aug. 2, 1940, the patient complained of substernal pain, with radiation to the arms, of four months' duration. At the outset the pain was felt on walking and relieved by rest. During the preceding six weeks, however, anginal pain occurred twice at night, and lasted about fifteen minutes. After rest in bed for eight days the nocturnal attacks subsided. An electrocardiogram taken six weeks after the first occurrence of anginal pain of rest (Fig. 2, *E*) showed a convex S-T segment and a shallow, inverted T wave in Lead I, and sharp inversion of T_4.

After a period of angina pectoris of effort of four months' duration, this patient had two anginal attacks during rest, neither of which lasted more than fifteen minutes. The electrocardiographic changes pointed to anterior wall infarction.

The clinical and laboratory data in the cases which were the object of this study are presented in Table I. The cases can be divided into two groups. Group I comprises Cases 1 through 9, in which myocardial infarction was associated with angina of effort. Group II includes Cases 10 through 16, in which evidence of myocardial necrosis was observed after brief attacks of angina of rest. In both groups the presence of myocardial infarction was suggested by fever and leucocytosis or increased sedimentation rate, or by a combination of these signs with anginal manifestations. Significant electrocardiographic changes were observed in all cases but one (Case 1). In the latter, the electrocardiogram was normal during the period of angina of effort, but the sedimentation rate was markedly increased. Significant electrocardiographic changes developed a few weeks later, in association with brief anginal attacks of rest. Finally, there were severe and protracted anginal attacks which were typical of myocardial infarction; necropsy revealed old and recent, extensive myocardial necrosis.

Among the electrocardiographic changes, inversion of T_4 was most frequent (nine cases). It was accompanied by inversion of T_1 in six

cases, and by a flat T_1 in two instances. It must be mentioned that in none of these cases was there electrocardiographic evidence of left ventricular strain; there was no depression of S-T in Lead I, and, when T_1 was inverted, its limbs were symmetrical. In one case, the T wave was inverted in all of the standard leads. A deep Q wave in Leads II and III was observed in four instances. Progressive changes in serial electrocardiograms were noted in four cases.

The electrocardiographic abnormalities and other clinical evidence of myocardial necrosis did not differ essentially in the two groups. Next to the electrocardiogram, the sedimentation rate underwent significant changes most frequently. A rapid sedimentation rate, varying from 21 to 71 mm. (Westergren), was observed in nine cases. Leucocytosis was present in five instances. Rise in temperature was noticed in three cases.

Angina of effort was the outstanding symptom in Group I; brief anginal attacks of rest were the prominent clinical feature in Group II. There was some overlapping of these symptoms, however, in the two groups. In two cases of Group I (Nos. 1 and 4), angina of effort, with laboratory evidence of myocardial necrosis, was followed by angina of rest, and, in one case of Group II (No. 15), angina of rest was preceded, in an interval of a few days, by the sudden development of severe angina of effort.

Angina pectoris of effort, which was the significant symptom in Group I, presented certain characteristics which seem to be essential in the diagnosis of progressive coronary insufficiency and ischemic myocardial necrosis. The onset of pain was often abrupt; one patient (Case 2) remembered the exact date when she had first experienced pain on effort. In another case (No. 6), in which angina of effort had been present for some time, myocardial infarction was accompanied by a sudden increase in the severity of the symptoms. The patient, who formerly had been able to walk three blocks before anginal pain occurred, complained suddenly that walking only one-half block caused severe distress. At the same time, serial electrocardiograms showed progressive changes indicative of anterior wall infarction. In addition to sudden changes in the functional capacity of the heart, the absolute amount of effort which causes anginal pain seems to be of diagnostic importance. Seven patients in Group I reported that walking one-half to three blocks produced angina pectoris. Such greatly diminished coronary reserve, in our experience, is usually associated with recent or past myocardial infarction.

In Group II, anginal attacks at rest were the first anginal manifestation in three cases (Nos. 13, 14, 16). In five instances, the onset of angina of rest was preceded in intervals of one week to twelve months by common angina pectoris of effort. The number of brief attacks of angina of rest which characterized the phase of myocardial necrosis varied from two to twenty; they lasted from a few seconds to twenty

TABLE I

ANALYSIS OF 16 CASES OF ATYPICAL ANGINAL PAIN WITH EVIDENCE SUGGESTIVE OF ISCHEMIC MYOCARDIAL NECROSIS

CASE	AGE	SEX	ANGINAL MANIFESTATIONS	EVIDENCE SUGGESTIVE OF ISCHEMIC MYOCARDIAL NECROSIS	NECROPSY OBSERVATIONS	REMARKS
1. J. B.	64	♂	In 1932, attack of anginal pain diagnosed as myocardial infarction. In March, 1941, sudden onset of severe angina pectoris of effort. In April, 1941, anginal attacks at rest, lasting 10 to 20 minutes, relieved by nitroglycerin. On April 30, 1941, a severe protracted anginal attack, followed by pericardial friction rub. Another severe attack resulted in progressive heart failure and death, on May 22, 1941	In March, 1941, during the period of severe angina of effort, sedimentation rate markedly increased. Leucocytosis. Normal electrocardiograms. In April, 1941, during the period of brief anginal attacks of rest, the electrocardiogram showed flattening of T_1, increase in the voltage of T_3, and inversion of T_4	Fibrosis and thinning of the apical area of the left ventricle. Multiple recent infarctions in the left ventricle due to thrombotic occlusion of the arteriosclerotic ramus descendens anterior of the left coronary artery	
2. E. S.	52	♀	Sudden onset of angina pectoris of effort on Aug. 1, 1941. Patient could not walk one block without experiencing pain. No pain at rest	Sedimentation rate (Westergren), tested twice in December, 1941, was 55 and 40 mm., respectively. Electrocardiogram (on Dec. 11, 1941) showed shallow inversion of T, with slightly elevated S-T in Lead I, and sharp inversion of T_4		Father and mother died from heart disease in their fifties
3. M. S.	66	♂	For four years angina pectoris of effort. Never anginal pain on rest	Electrocardiographic changes: deep Q and inverted T in Leads II and III, suggestive of posterior wall infarction		

4. P. S.	52	♂	Sudden onset of angina pectoris of effort in November, 1941. The attacks increased in severity. In February, 1942, a severe anginal attack occurred, lasting one-half hour. Since then frequent pain attacks during rest, all short and relieved by nitroglycerin. Sudden death five months after the onset of anginal complaints	During the period of angina of effort: Sedimentation rate (Westergren) 48 mm. An electrocardiogram showed isoelectric T_1 and sharp inversion of T_4. These changes subsided during the following two months, but the sedimentation rate remained high (67 mm. on March 28, 1942)		Brother died from coronary attack at the age of 55 years. Patient suffered from hypertension
5. J. K.	57	♀	Since second week of February, 1941, severe angina of effort. Walking one block caused precordial pain. No angina of rest	Sedimentation rate (Westergren) on March 21, 1941, was 32 mm. An electrocardiogram taken March 11, 1941, showed isoelectric T_1 and sharp inversion of T_4. After eleven months, when the patient was reexamined and her condition was found improved, a normal electrocardiogram was obtained		
6. B. N.	48	♀	Since July, 1940, angina pectoris of effort. Since January, 1941, walking only one-half block caused anginal pain. No angina of rest	Electrocardiogram taken Jan. 28, 1941, showed inversion of T_1 and T_4. These changes were progressive. Sedimentation rate (Westergren) on Jan. 21, 1941, was 21 mm.		
7. M. G. L.	56	♂	Following "flu" in August, 1938, angina pectoris of effort developed. There was never pain at rest	Electrocardiogram taken five months after the "flu" showed the signs of anterior wall infarction		
8. S. S.	62	♀	Since June, 1941, severe angina of effort. Walking one-half block caused anginal pain. Never pain during rest	Sedimentation rate (Westergren) in August, 1941, was 74 mm. Electrocardiogram (July 29, 1941) showed convex S-T segment and inversion of T in Lead I, also negative T in Leads II and III		Complicating diseases: Diabetes and hypertension

TABLE I—CONT'D

CASE	AGE	SEX	ANGINAL MANIFESTATIONS	EVIDENCE SUGGESTIVE OF ISCHEMIC MYOCARDIAL NECROSIS	NECROPSY OBSERVATIONS	REMARKS
9. M. A.	30	♀	Since August, 1941, severe angina pectoris of effort. Walking one or two blocks caused anginal pain. Never pain during rest	Leucocyte count (Nov. 13, 1941) was 12,400. Electrocardiogram (Sept. 13, 1941) showed deep Q_2 and Q_3 and inversion of T_3. The same changes in subsequent tracings		Complicating disease: Mitral regurgitation. Mother died from hypertension at the age of 36 years
10. H. J.	52	♂	Since early 1941 angina pectoris of effort. Two weeks after gastrectomy (on Nov. 4, 1941), anginal attacks occurred repeatedly during rest, each lasting about ten minutes	Temperature rose to 101.4° F. a day after the onset of anginal attacks of rest. The sedimentation rate (Westergren) increased to 37 mm. The heart sounds were distant. Progressive electrocardiographic changes suggested anterior wall infarction		Complicating condition: Hypertension
11. W. L.	48	♂	Since April, 1940, substernal pain on walking. Two brief anginal attacks, lasting fifteen minutes, occurred in the middle of June, 1940, during night	Electrocardiogram (Aug. 2, 1940) showed a convex S-T and inverted T in Lead I, and sharp inversion of T_4		
12. J. F.	68	♂	Since the beginning of 1942 tightness of the chest on walking 3 or 4 blocks. In the second week of June, 1942, walking only one block caused severe pain in the chest. Anginal attacks came also during rest, lasting up to fifteen minutes. The patient felt "worn out"	Leucocyte count (June 16, 1942) was 12,000. The electrocardiogram taken on the same day showed isoelectric T_1, absence of R_4, sharp inversion of T_4, and deep Q waves in Leads II and III		

13. H. G.	63	♂	Never angina pectoris of effort. Ten days after an abdominal operation (on May 7, 1942), attacks of substernal pain developed during rest, relieved by nitroglycerin. The attacks were brief due to the effect of nitroglycerin, and came about twice daily for two weeks	Temperature rose to 100° F. on the first day of the anginal attacks. Three days later the sedimentation rate (Westergren) was 34 mm. An electrocardiogram on May 23, 1942, showed flattening of T_1 and flattening and late inversion of T_4. These changes subsided within two weeks		
14. S. M.	62	♀	Never angina of effort. Very brief attacks of precordial pain developed in the middle of August, 1941, lasting a few seconds to a few minutes. These attacks occurred repeatedly during a period of six weeks, while the patient was at rest	Temperature rose to 100.2° F. on the first two days following admission (Sept. 26 and 27, 1941). Sedimentation rate (Westergren) on Sept. 29, 1941, was 23 mm. Leucocyte count, on Sept. 27, 1941, was 10,600. Four electrocardiograms, taken between Sept. 29 and Oct. 20, 1941, showed progressive changes resulting in inversion of T_1 and T_4		Complicating condition: Hypertension with marked hypertrophy of the left ventricle
15. L. K.	55	♂	Sudden onset of angina pectoris in May, 1942, when patient lifted a load; the pain lasted only a few minutes. In the following week three short anginal attacks during meals or excitement, none lasting more than a few minutes	Electrocardiogram (May 14, 1942) showed elevation of S-T in Lead III and depression of S-T in Lead I; also marked depression of S-T and flattening of T in Lead IV. In the following weeks, T_4 became inverted and a Q wave developed in Lead IV		
16. L. R. G.	42	♂	In September, 1940, a nocturnal attack of severe substernal pain, lasting 15 minutes. A similar attack on the next day, while driving a car; this attack lasted 10 minutes. Then severe weakness developed. Thereafter angina of effort and sometimes short attacks during night. There was never an attack lasting more than 15 minutes	An electrocardiogram taken two years after the onset of angina pectoris showed nearly isoelectric T_1 and upright T_3		

minutes. In Case 16, angina pectoris started with two brief attacks during rest. The serious meaning of these symptoms was not recognized, and the necessary rest in bed was neglected. Thereupon, marked angina of effort developed, and the patient was unable to walk one block without experiencing pain. This is a frequent event after myocardial infarction. It is remarkable that anginal attacks of rest associated with evidence of myocardial infarction (in Case 13) were promptly abolished by nitroglycerin.

One patient in Group I (Case 1) died after new and severe anginal attacks had followed the development of angina of effort. Another patient in Group I (Case 4) died suddenly, five months after the abrupt onset of angina of effort. There was no fatality in Group II.

COMMENT

Our observations prove that angina of effort or brief attacks of angina of rest may be significant symptoms of ischemic myocardial necrosis. The practical importance of this fact with regard to management is obvious. Although the serious meaning of such atypical anginal attacks has been repeatedly mentioned in the literature, it has not been generally recognized.

Obrastzow and Straschesko[3] reported the case of a 57-year-old man who had myocardial infarction (proved by autopsy) which was clinically indicated by brief attacks of angina of rest, none of which lasted more than ten minutes. Herrick[4] has stated that ischemic myocardial necrosis of slight extent is clinically often indicated by mild anginal pain of rest. The difficulty of differentiating "angina pectoris" from minor forms of "coronary occlusion" has been stressed by Smith.[16] This author advised that "coronary occlusion" be considered whenever attacks of angina grow more severe than usual or come on at rest. Boas[17] has commented on patients who are ordinarily regarded as having common angina pectoris, but, on close questioning, admit that their complaints started with an anginal attack of particular severity, lasting not more than fifteen minutes. Such patients, in Boas' opinion, have, at the outset, suffered structural damage to the myocardium. Pardee[18] has discussed patients with electrocardiographic signs of myocardial infarction "who have never been subject to an attack which could have been due to coronary thrombosis." Our Case 7 is an example of this. After having grippe, the patient experienced angina of effort, but had never had a severe, protracted, anginal attack during rest. Electrocardiographic evidence pointed to myocardial infarction.

Bourne[19] observed a 61-year-old patient who, for four weeks, had experienced angina pectoris of effort, but not of rest; the electrocardiogram showed signs of anterior wall infarction. The author concluded that "clinically, coronary thrombosis is suggested by severe angina of effort coming on suddenly and slowly diminishing from the first on-

set." LeRoy and Snider[20] reported on a 49-year-old patient who had complained of precordial pain on effort for one week, and then suddenly died. Autopsy revealed old calcific occlusion of the main branches of the left coronary artery and "a slight softening of the apical region." Parkinson and Bedford[5] have expressed the opinion that gradual coronary occlusion, leading to scattered myocardial fibrosis, is clinically manifested by angina of effort which becomes more frequent and more easily induced. According to Blumgart and his co-workers,[21] particular care should be given to those patients "who suddenly develop angina of effort, mild or severe", and also to those "who, having had angina pectoris, experience a sudden aggravation of their symptoms." The authors hold that increased frequency and severity of anginal attacks denote progressive coronary insufficiency. A similar view has been expressed by Master and his associates[22] who, in a study on premonitory symptoms of acute coronary occlusion, found that a sudden onset or aggravation of angina of effort often presaged the development of myocardial infarction.

Various authors have reported on "premonitory pain in coronary occlusion."[5, 22-28] Myocardial infarction is often heralded by prodromal pain which occurs hours, days, or weeks prior to the "actual attack of coronary occlusion." The premonitory pain may be mild or severe, and it may last a few minutes or several hours. It is mostly unrelated to effort and not influenced by nitroglycerin. Occasionally, sudden onset or aggravation of angina of effort presages the development of myocardial infarction.[22, 28] It is readily seen that the description of premonitory pain fits well into the picture of anginal symptoms presented by the patients in our study. According to the authors who have reported on premonitory pain, the latter is distinguished from "coronary occlusion" by the lack of evidence of myocardial necrosis, such as fever, leucocytosis, rapid sedimentation rate, and significant electrocardiographic changes. However, some of this evidence was present in the cases in our report. Moreover, careful study of the cases reported by others occasionally reveals the presence of such evidence. A conspicuous number of those patients who were subjected to electrocardiographic examination during the stage of premonitory pain showed significant electrocardiographic changes. For instance, in two cases (No. 8, Fig. 2*b* and No. 15, Fig. 3*b*) reported by Feil,[23] there were electrocardiographic signs which are considered by some authors as indicative of myocardial infarction.[13-15] In a case reported by Master and his associates[22] (Fig. 4), there were electrocardiographic changes like those attributed by the same authors to myocardial infarction in the absence of acute coronary occlusion.[29] In Boyer's[28] Case 3, there was, during the stage of premonitory pain, in addition to an increased sedimentation rate, the electrocardiographic pattern of a low R_1 with a deep S_2 and S_3; there was also a flat T_1, with high voltage of T_3. These signs are suggestive of anterior wall infarction. In the

same author's Case 5 there were electrocardiographic signs "suggesting that there had been some change in the heart muscle" during the phase of premonitory pain.

Master and his co-workers[22] have stated that "premonitory pain" was invariably followed by "typical coronary occlusion." However, in some cases reported by Sampson and Eliaser,[25] such a sequence of events did not take place. In our group of cases, "prodromal pain" was only once (Case 1) followed by the typical clinical picture of myocardial infarction. Sampson and Eliaser and Master and his associates have stressed the difficulty of distinguishing premonitory pain from "actual coronary occlusion," especially in cases in which the premonitory pain was severe and protracted. Our own experience and the evidence offered in the reports of others[22, 23, 28] suggest that such a distinction is often artificial. "Premonitory pain" usually indicates progressive coronary insufficiency, and is most often associated with ischemic myocardial necrosis which may or may not be followed, after a period of days or weeks, by more extensive myocardial infarction.

Atypical anginal pain like that in the cases of our report is probably associated with myocardial necrosis of lesser extent; it is possibly due to sudden occlusion of small coronary branches,[4, 11] or to gradual narrowing of coronary arteries.[6, 21] It should be mentioned that electrocardiographic changes which are often associated with massive infarction, such as a high take-off of S-T in Lead I, absence of R_4, and low voltage of QRS in the standard leads, were lacking in our cases. Postmortem examination in cases of coronary arteriosclerosis often reveals the presence of small areas of fibrosis which had escaped clinical diagnosis. It is likely that the anginal symptoms in the cases of our report represent the clinical counterpart of these anatomic changes.

The practical implications of recognizing the serious meaning of atypical, mild anginal attacks are obvious. Although it is unlikely that complete occlusion may be obviated by rest in bed in cases of progressive coronary thrombosis, it is generally agreed that the deleterious effect of inadequate blood supply to the myocardium is reduced by diminishing the strain on the heart. This is particularly true when myocardial infarction develops in the absence of occlusion, which happens in about 30 per cent of the cases of myocardial infarction.[30] Strict rest in bed should be instituted whenever a sudden onset or aggravation of angina of effort, or the appearance of brief attacks of anginal pain during rest, points to progressive coronary insufficiency.[11, 16, 20, 21, 28] In such cases, ischemic myocardial necrosis is often present, as is suggested by the observations of this study. Sudden death is most frequent among cases of unrecognized myocardial infarction in which there are only mild symptoms.[4, 11, 17, 20] Experimental and clinical evidence suggests that death is often due to ventricular fibrillation caused by reflex vasoconstriction of the coronary arteries, which is in-

duced from the infarcted area.[20] Therefore, the use of vasodilators, such as atropine, aminophylline, and papaverin, during the early stage of myocardial infarction has been advised as a lifesaving procedure.

A thorough history is of paramount importance in the recognition of progressive coronary insufficiency which may early result in the formation of small areas of necrosis. One should not be satisfied with the plain diagnosis of angina of effort. It is indispensable in every case to ascertain the present and past functional capacity of the heart, i.e., the amount of effort that produces anginal pain. Any sudden change in the functional capacity indicates progress of the coronary disease, and this demands complete rest in bed for at least three weeks, until collateral circulation has developed to supplement the deficient blood supply.[34, 35] Anginal attacks during the night or after meals (in the absence of any additional effort) should also be considered as warning signals. A suspicion aroused by the history is often supported by finding that the sedimentation rate is increased. This is occasionally a more sensitive index of myocardial necrosis, when other causes can be ruled out, than the electrocardiogram,[31] and "may presage a coronary attack by weeks and months."[32] It is of interest that Riseman and Brown[33] have observed an increase in the sedimentation rate in more than 50 per cent of cases of angina pectoris. They expressed the opinion "there is reason to believe that attacks of angina pectoris occasionally result in myocardial damage." Lack of electrocardiographic changes should by no means be a reason for abandoning a diagnosis of myocardial infarction which is otherwise clinically well founded. In view of the serious dangers involved in neglecting the warning symptoms of progressive coronary insufficiency, I would subscribe to the advice of LeRoy and Snider:[20] "Suspicion rather than certainty should determine the psysician's conduct."

SUMMARY

This is a report of sixteen cases in which there was clinical and laboratory evidence suggestive of myocardial infarction, although characteristic, severe, and protracted anginal attacks were lacking. In nine cases, myocardial infarction was indicated by the sudden onset or aggravation of angina of effort; in seven instances, it was clinically signalized by brief attacks of angina of rest, lasting up to twenty minutes. Similar observations are quoted from the literature.

The seriousness of such atypical anginal manifestations is often unrecognized, and proper management of the patients is neglected. Sudden death is frequent among this group of cases. A painstaking history, including an accurate estimate of the functional capacity of the heart and a comparison of present and past performances, furnishes the most significant diagnostic data. An increase in the sedimentation rate is often a more sensitive index of myocardial necrosis than are electro-

cardiographic changes. Lack of the latter should never be considered as conclusive evidence against serious myocardial involvement.

Anginal pain like that in the cases in our report has often been designated as "premonitory pain," which precedes the development of "actual myocardial infarction." Our own experience and reports in the literature prove that "premonitory pain" is not invariably followed by typical anginal attacks signifying myocardial infarction. Moreover, "premonitory pain" is often by itself associated with evidence of myocardial necrosis. Hence, it appears that the distinction between "premonitory pain" and "actual myocardial infarction" is inappropriate. A sudden onset or aggravation of angina of effort, or brief attacks of angina of rest indicates progressive coronary insufficiency, and is in the majority of cases, associated with ischemic myocardial necrosis.

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CONTINUOUS RECORDING ELECTROCARDIOGRAPHY

WILLIAM B. LIKOFF, M.D., MAURICE B. RAPPAPORT, E. E., AND SAMUEL A. LEVINE, M.D.
BOSTON, MASS.

INTRODUCTION

DURING the past few decades electrocardiographic apparatus has developed very rapidly. From delicate, cumbersome instruments the machines have become sturdy and compact, so that, whether they use the original string technique or the amplifying tube, they are now readily portable. None of the mechanical refinements, however, has made it possible to record an electrocardiogram continuously over a long period of time. There are important occasions when such data are desirable. With this in mind, a continuous recording electrocardiograph has been devised.

The nearest approach to what may be considered continuous recording is the Asher-Hoecker apparatus,[1] which produces a fluorescent electrocardiographic image that fades out in less than one minute. The duration of a visible electrocardiographic complex or of several succeeding cardiac cycles, therefore, is limited by the persistence of fluorescence. The Asher-Hoecker "Cardioscope" is a useful instrument in many ways, but is inadequate for detailed electrocardiographic analysis. The gradual or instantaneous transitions, which require precise analysis, are limited to less than a minute of observation, and thereafter the image is completely lost. Furthermore, it is inconvenient, if not physically impossible, to view fluorescent electrocardiograms constantly for prolonged periods of time and to describe in detail all that has happened. This may be partially circumvented by simultaneously taking short records with the ordinary electrocardiograph, but gradual transitions are permanently lost, and the constant presence of a competent observer is required.

DESCRIPTION OF APPARATUS*

Some of the continuous electrocardiographic registrations may last as long as twenty-four hours. The ordinary instrument is incapable of continuously registering cardiac action potentials over such a long period of time because of electrical and camera limitations. We will first consider the camera mechanism and the problems involved.

Camera.—At the customary electrocardiographic speed of 25 mm. per second, the film consumption is 300 feet per hour, or 7,200 feet in twenty-

From the Research Laboratories of the Mount Sinai Hospital, Phila., the Medical Clinic of the Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School, Boston.

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four hours. As far as we know, the largest roll of film commercially available is approximately 175 feet long, and not all of that roll can be absorbed by the exposed record container. Even if it is assumed that a 175-foot roll of film could be run through the camera mechanism continuously, it would be sufficient for only a 35-minute record. If a camera were devised to accommodate the huge 7,200-foot roll of film required for twenty-four hours of operation, many obstacles of a serious nature would still be present. For example, the physical dimensions of the

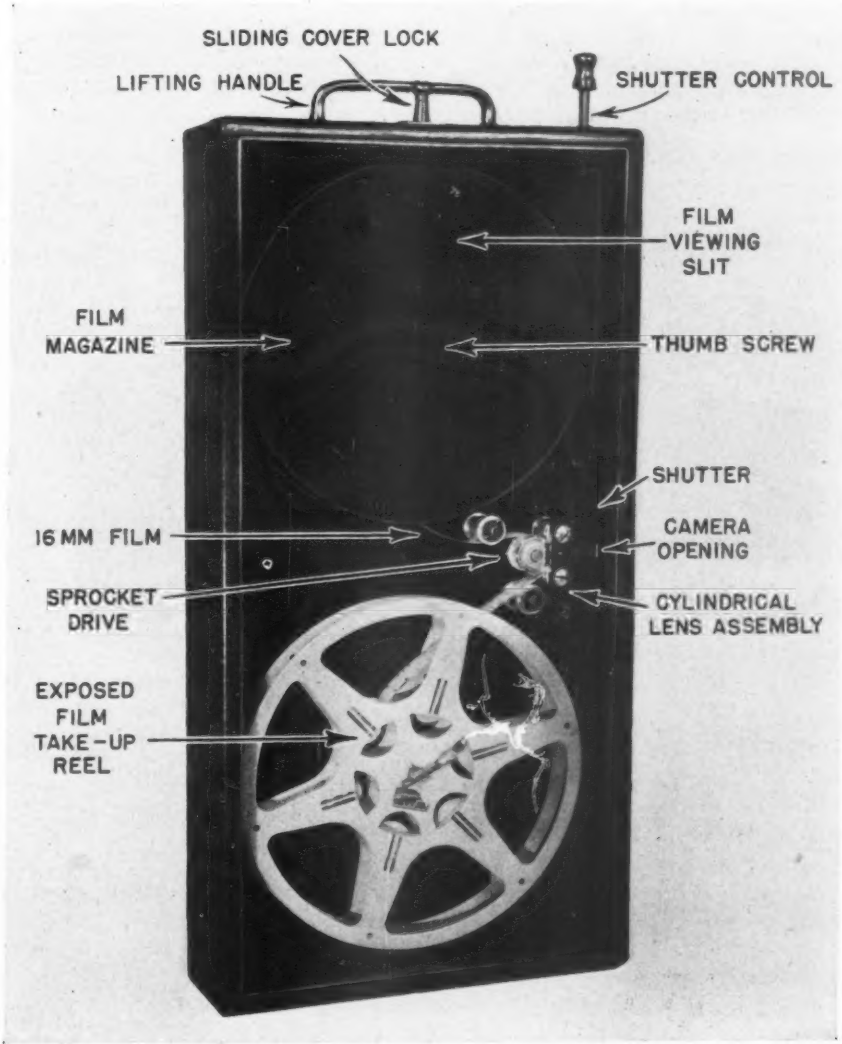

Fig. 1.—Photograph of the camera mechanism with the light-proof sliding cover removed.

camera would make it unwieldy. Proper lengths of film or bromide paper would not be commercially available except, possibly, on special order. The film cost would be high, and the developing, processing, and handling problems would be difficult.

It was decided that a solution to the problem would be to devise an electrocardiographic apparatus capable of registering the action potentials in miniature on 16 mm. moving picture film. The miniature record could then be studied with the aid of a photographic enlarger or projector, which would reproduce the electrocardiogram in normal dimensions. Four-hundred-foot rolls of 16 mm. film are standard and commercially available. If a twentyfold over-all reduction is made in the size of the recorded electrocardiogram and in film speed, 400 feet of film are sufficient for 26.7 hours of continous operation. The effective or workable width of the 16 mm. film is 10 mm., for the sprocket holes consume 6 mm. Therefore, at a twentyfold reduction in the deflection amplitudes of the complexes, the 10 mm. working width is actually the equivalent of 20 cm. film with normal electrocardiographic deflection amplitude (one centimeter per millivolt).

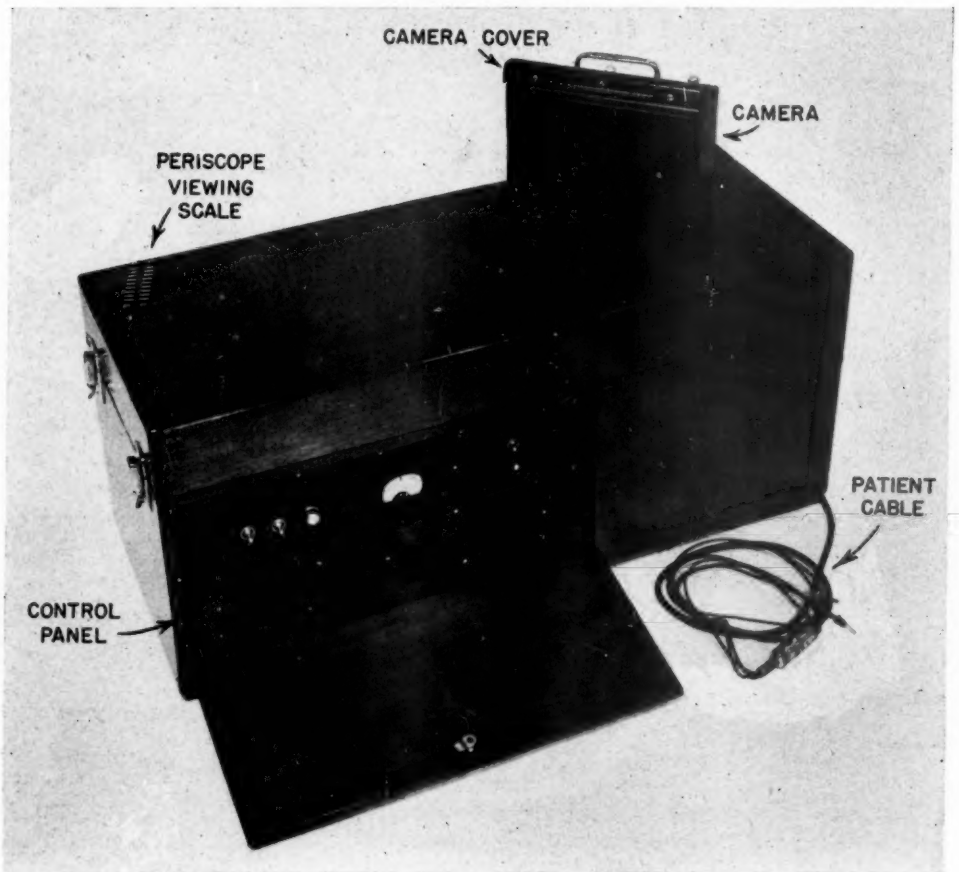

Fig. 2.—The continuous recording electrocardiograph.

Fig. 1 is a photograph of the camera mechanism, with the light-proof sliding cover removed. The roll of 16 mm. film is placed in the magazine and threaded through the guide rollers and sprocket drive to the exposed film take-up reel. The sprocket is connected to a synchronous motor by means of a gear train. When the camera is lowered into the electro-

cardiographic mechanism (Fig. 2), the gear coupled to the sprocket engages another gear which is directly coupled to the synchronous motor. The exposed film take-up reel is connected to the sprocket by means of a pulley system and spring belt. A synchronous, alternating current motor drive is used because its speed is constant under all conditions of operation. The timing of the electrocardiogram is based upon the speed at which this motor rotates. The rotation of the motor causes the sprocket to rotate in a clockwise direction. This action pulls the film from the magazine to the exposed take-up reel past the camera opening and cylindrical lens assembly. The spring belt drive connecting the sprocket and take-up reel is so designed as to keep the film under tension. As a result, the exposed film winds up into a snug roll on the reel. The shutter control is merely a device to close the camera opening when carrying the camera to and from the darkroom.

The Optical System.—Fig. 3 is a schematic sketch of the optical system and the other major components of the continuous recording electrocardiograph. The optical system is composed of two independent galvanometric channels; one is used for recording, and the other for viewing and standardization. A viewing channel must be used in which the deflections are exactly twenty times as large as the deflections of the recording beam, for it is impossible to judge and calibrate the instrument when 1 mv. deflects the recording beam only ½ mm. The optics of the recording channel are of an unorthodox design; this is necessitated by the unusual and exacting requirements of miniature electrocardiographic photography. The record must be extremely sharp and well defined, for the minutest flaw, when magnified twenty fold for visualization, may be sufficient to mar completely the legibility of the electrocardiogram. The cylindric or camera lens arrangement must be capable of focusing the recording beam down to a slit of light 0.0005 inch in thickness. Furthermore, this adjustment must remain fixed for the life of the instrument.

The schematic sketch (Fig. 3) indicates the manner in which the recording beam impinges upon the film. The recording condenser lens picks up a portion of the light which radiates from the incandescent lamp. The positioning and focal length of the condenser lens are such that it throws a minute image of the lamp filament through the recording optical slit to a point slightly behind the concave recording galvanometer mirror (the theoretical location of the focused image if the mirror were removed). In turn, the concave mirror reflects the beam of light and diverges it so that an image of the recording optical slit falls upon the front surface of the cylindric lens assembly. The latter squeezes the beam down to a slit of light 0.0005 inch, or less, in height; the width of the beam remains unchanged, and is dependent upon the degree of opening of the recording optical slit.

When a cardiac action potential is applied to the moving coil (d'Arsonval) galvanometer after passing through the electrocardiographic amplifier, the galvanometer coil supporting the concave mirror deflects that amount which is directly proportional to the intensity of the action potential. The motion of the galvanometer causes the 0.0005 inch slit of light to move horizontally across the film. The combination of the downward motion of the film and the transverse movement of the slit of light produces the miniature electrocardiogram.

The width of the isoelectric line is proportional to the opening of the recording slit; the greater the opening the wider the line. If the

galvanometer is stimulated by a slowly changing phenomenon, such as a P or T wave, the 0.0005 inch slit deviates from the isoelectric level at a slow rate, and the registering beam is slightly narrower than during the isoelectric phase (Fig. 4). The more rapid the deviation from the isoelectric level, the narrower the line becomes. Therefore, a QRS complex registers as a narrower line than a P or T wave. An infinitely fast deviation, such as would occur upon standardization during the transition interval, with an infinitely fast galvanometer, would produce a registration thickness equal to that of the slit of light.

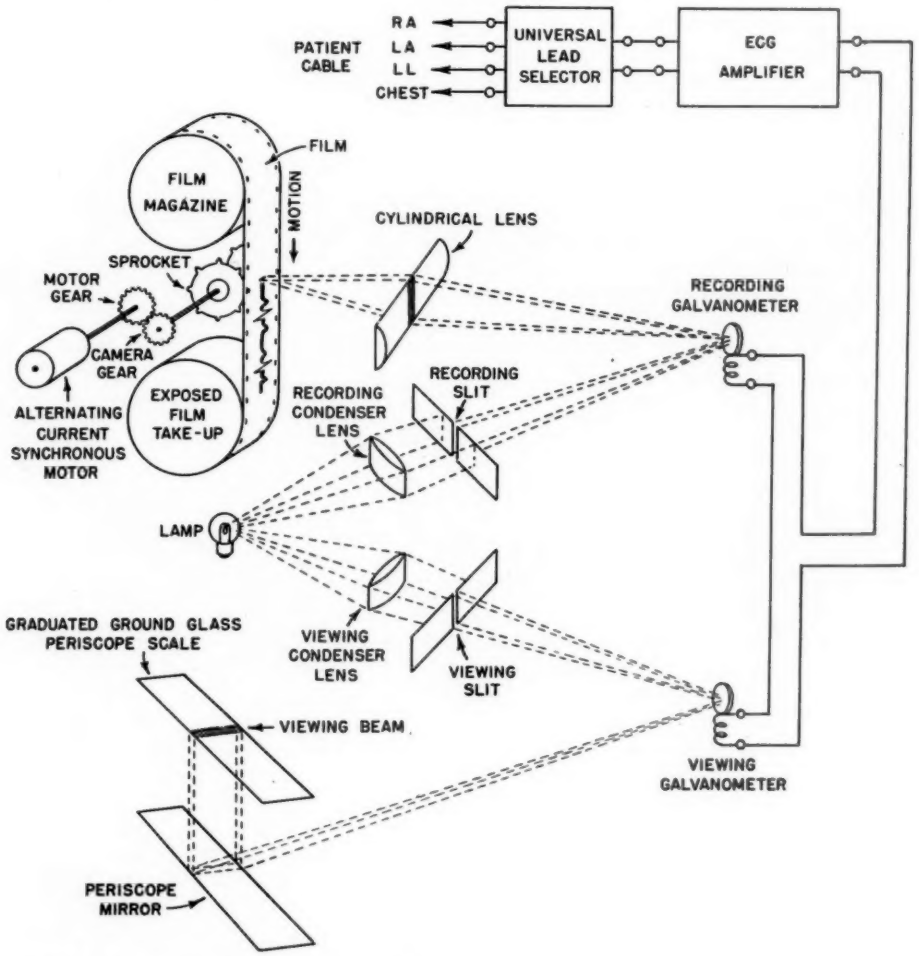

Fig. 3.—Schematic sketch of the optical system and other major components of the continuous recording electrocardiograph.

It was previously mentioned that, in miniature electrocardiography, it is essential to focus the recording beam down to a sliver of light 0.0005 inch, or less, in thickness in order to obtain good QRS definition. To illustrate, consider a condition in which a rather short QRS complex of 0.06 second is registered by a slit of light more than 0.0005 inch in thickness. At normal film speed (approximately one

inch per second), the base of the 0.06 second QRS complex is equal to 0.06 inch. In a miniature electrocardiogram, in which the over-all

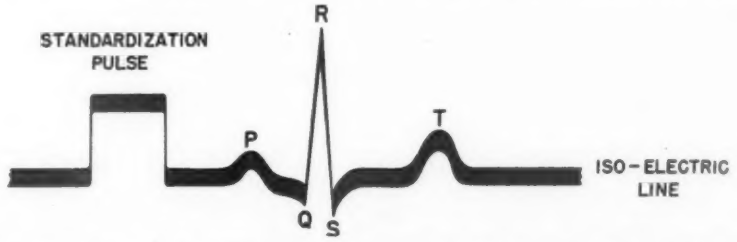

Fig. 4.—Sketch to illustrate variation in the recorded thickness of electrocardiographic complexes as a function of deflection speed.

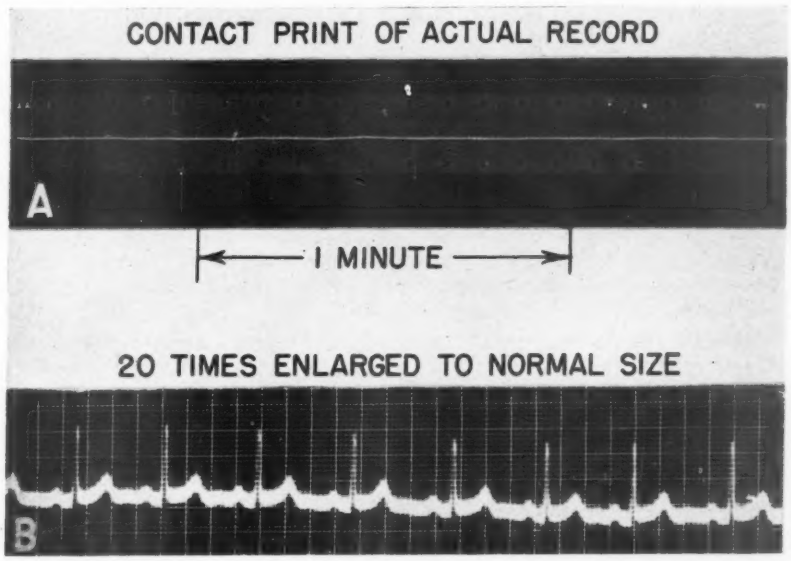

Fig. 5.—A comparison of an actual tracing and the normal electrocardiogram which was obtained by enlarging the miniature record.

dimensions of the complexes are one-twentieth normal in size, the QRS base is equal to 0.003 inch. The cylindric lens of a good commercial electrocardiograph will focus the light down to approximately 0.004 inch instead of 0.0005 inch. If a summation is made of the Q-R and R-S segments registered by a 0.004 inch sliver of light, and we take into consideration that the duration of a QRS complex is not sufficiently short to allow for the thinning out of the lines to even 0.004 inch, the Q-R and R-S segments must exceed 0.008 inch. Such registration lines are but a fraction of the actual duration of the QRS wave at a film speed of 25 mm. per second, but in miniature electrocardiography the base of the QRS complex is only 0.003 inch for a 0.06 second interval. Therefore, if a sliver of light 0.004 inch in thickness were used for recording the miniature graph, the thickness of the Q-R or R-S complex would be more than the actual QRS duration, and a blotch would result instead of a well-defined QRS complex. We have found that a 0.0005 inch beam of light produces well-defined electrocardiograms on

all human beings. The finer the focus, however, the better the photographic definition.

Fig. 5*B* is a twentyfold enlargement of the miniature electrocardiogram shown in Fig. 5*A*, which was made with a focal precision somewhat better than 0.0005 inch. In some of the subsequent figures a slight degree of "fuzziness" may be seen in the shorter QRS complexes. The slower P and T waves are unaffected and sharp. The lack of sharpness in the short QRS complexes does not interfere with the correct interpretation.

The viewing channel optical system is orthodox in design. The ground glass viewing scale is calibrated in centimeters and the instrument is standardized by adjusting the degree of electronic amplification so that the application of 1 mv. to the amplifier input circuit deflects the viewing beam 1 cm. The recording and viewing galvanometers are electrically interconnected in series to the amplifier output. The recording galvanometer sensitivity is adjusted so that it deflects exactly 0.05 cm. when the viewing galvanometer beam deflects exactly 1 cm. This galvanometric ratio is always a constant.

Electrocardiographic Considerations.—The continuous recording electrocardiographic channel must satisfy all of the following operational conditions:

1. The over-all sensitivity of the apparatus must not vary during an electrocardiographic run. Even slight variations in the sensitivity calibration cannot be tolerated during the longest possible recording period of 26.7 hours.

2. Patient resistance, which is a variable over long periods of time, must not affect the operation and sensitivity of the electrocardiograph.

3. Skin potentials must be automatically compensated, or the recording beam may drift beyond the recording limits of the camera.

4. The isoelectric level must not be susceptible to any appreciable drift for the duration of the record.

5. The apparatus must be free of internal alternating current interference, and be capable of automatically eliminating induction effects from external wiring, diathermy machines, roentgen-ray equipment, etc.

6. The instrument must be capable of operating from the house lighting system. Batteries are not practical for continuous operation.

7. The over-all electrocardiographic requirements must satisfy all the accepted standards.

8. The electrocardiograph must be capable of functioning for the duration of the test without the attention of an operator.

A galvanometer that uses the Einthoven recording technique (quartz string galvanometer) does not satisfy requirements 1, 2, 3, 4, and 8. The usual type of electrocardiograph amplifier and mirror galvanometer combination does not satisfy requirements 1, 4, 6, and 8. A specially designed amplifier and mirror or d'Arsonval galvanometric system had to be devised to satisfy all of the eight conditions fundamental to continuous electrocardiography. The characteristics of an Einthoven string galvanometer are not sufficiently flexible for such modifications.

The amplifier is of the resistance-capacity coupled variety.[2-4] The time constant of the amplifier is approximately 2.5 seconds. For more than 0.2 second the amplifier does not exhibit any decay, and thereafter the decay is gradual and a function of the time constant.[4-6] The 0.2 second,

during which there is no decay, is longer than the duration of any known human electrocardiographic complex. The galvanometric speed is approximately 0.01 second.

It was a difficult problem to satisfy the listed requirements and utilize commercial power lines as a source of energy. The average 110-volt power line may vary between 105 and 120 volts during a twenty-four-hour period, and, in addition, instantaneous variations to the extent of several volts are constantly occurring. These fluctuations must be regulated before application to the amplifier system, or they would register graphically in superposition upon the electrocardiogram. Since these fluctuations are several thousand times as large as cardiac action potentials, they would completely mar the record and drive the recording beam beyond the bounds of the camera. Likewise, the sensitivity of the amplifier would vary with the slow line voltage variations. These voltage changes were regulated to a point at which maximum fluctuations, whether instantaneous or gradual, produced insignificant deviations of the isoelectric line and created zero changes in the amplifier sensitivity. This was accomplished by electronic regulation, the only known system capable of responding instantaneously to fast and gradual line voltage variations, and requirements *1*, *4*, and *6* were adequately met.

The resistance-capacity type of electronic amplification satisfied requirements *2* and *3*.[5, 6] Requirement *5* was met by an automatic balancing method which eliminates only the electrical disturbances external to the patient. Requirement *7* was satisfied by designing an amplifier with a 2.5 second time constant, a 0.2 second straight line characteristic, and a galvanometric speed of 0.01 second. A lead selector switch was devised which could select, in addition to the conventional leads, CR, CL, CF, and the Wilson indifferent lead. A synchronous motor was used for timing.

The Enlarger.—To study the miniature electrocardiograms and to make photographic enlargements of sections of a continuous record, the instrument shown in Fig. 6 was devised. It consists of a good quality enlarging head, with a built-in 16 mm. film carrier and guide. The film which is mounted on a rewind reel is threaded through the film carrier and guide and then attached to the second rewind reel. The film may be run to and fro through the enlarging head, depending upon which rewind is operated. Exactly twentyfold optical enlargements must be made to obtain electrocardiograms with standard dimensions. To do this with an ordinary enlarging lens, the distance between lens and viewing screen or sensitized paper must be more than is customarily used in photographic work. Furthermore, the rewind reels and viewing screen cannot be separated by too great a distance, for the observer must operate the reels and view the graph simultaneously. A reasonable distance between the enlarged image and the observer's eyes was found to be approximately 14 inches. These qualifications were met by a system of mirrors. After the light leaves the enlarging lens (Fig. 6) it is directed to mirror *A*, which reflects it to mirror *B*, which, in turn, throws the image on the viewing screen or sensitized paper. Without such a system, the height of the apparatus would be approximately three times as great, and the separation between rewind reels and viewing screen would be increased in the same ratio.

The microfilm operating technique is practically identical with that required in making ordinary photographic enlargements, or in viewing by means of a projector.

APPLICATIONS

Continuous electrocardiography has definite applications. There are certain aspects of the mechanism of the arrhythmias that can readily be studied and clarified by this method. It is often difficult to actually photograph the beginning and ending of such disturbances as paroxysmal tachycardia, fibrillation, and flutter. The very last or first complex of

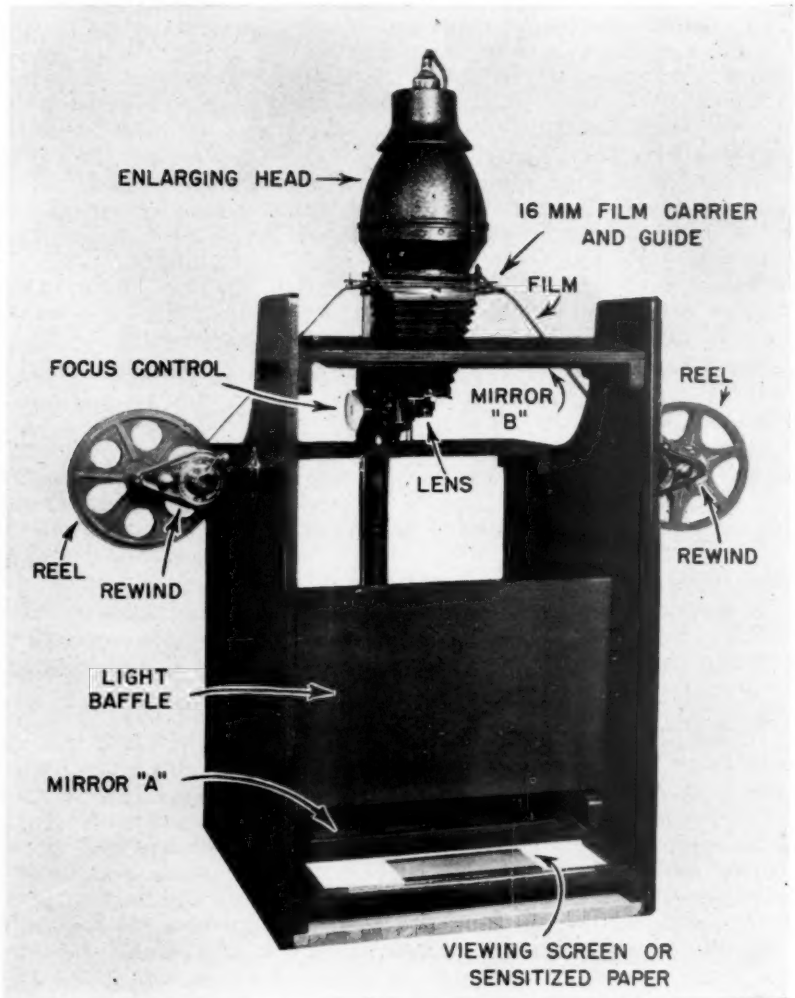

Fig. 6.—The enlarger.

such paroxysms may be the critical point in affording an explanation for the mechanism involved. Although such transitions have frequently been recorded, they generally have occurred as a result of deliberate manipulations, such as vagal stimulation, or the administration of drugs. It would be valuable to have more information concerning the spontaneous changes that occur under such circumstances, and

these are obtained only with difficulty except by continuous electrocardiography. Even the minute and detailed effects of drugs, especially intravenous therapy, on the electrocardiogram and on arrhythmias can become available for closer scrutiny.

Other observations of a more prolonged type, in which either the exact rate of the heart or the changes in the electrocardiogram itself need to be observed, could readily be investigated. The effect of labor pains, or labor itself, on both the mother's heart and the fetal rate, the effect of anesthesia in prolonged operations, the changes occurring during sleep, or during flights at high altitudes with low oxygen tension, and many other similar problems readily lend themselves to this study. Finally, it has become a matter of considerable interest to study the mechanism of death, especially in cardiac disease. Although records have been occasionally obtained which indicate that ventricular fibrillation is the terminal event in sudden death due to coronary artery disease, more often the tracings that have been recorded when patients died were those taken after death had occurred. Furthermore, there is reason to believe that sudden death may be the result of an inhibition of contractions such as occurs in asystole accompanying Adams-Stokes disease, and not due to ventricular fibrillation. This problem is one that can be satisfactorily studied only by prolonged continuous electrocardiography.

RESULTS

Eighteen continuous electrocardiographic tracings, from thirty-five minutes to ten hours in length, have been recorded. Three were obtained while a patent ductus was being ligated, and eight were terminal tracings taken from one to six hours before death, until there was no longer any evidence of cardiac electrical activity. Of these eight, three patients were dying of coronary thrombosis and myocardial infarction, two of rheumatic valvular disease, and one each of constrictive pericarditis, nephritis and spontaneous potassium poisoning, and pneumonia. The remaining records were from patients with arrhythmias, and included two instances of paroxysmal ventricular tachycardia, two of complete heart block with typical Adams-Stokes seizures, and one each of auricular fibrillation, auricular flutter, and a bigeminal rhythm caused by ventricular extrasystoles.

In those cases in which a patent ductus was ligated, no specific changes were seen in the continuous electrocardiogram which could be attributed to the correction of the cardiac abnormality. Transient arrhythmias and an increase in the amplitude of the ventricular complexes were observed, but these developed prior to the ligation, and were caused either by the anesthesia, manipulation, or change in the position of the heart. A typical record is illustrated in Fig. 7. The three limb leads taken just before anesthesia are shown in *A*, while *F* and *G* are the standard leads obtained immediately upon, and one hour after, ligation. It is seen that the nodal

beats (*B*), sinus tachycardia (*C*), nodal tachycardia (*D*), variations in T-wave amplitude, gradual development of a small S wave, and increase in QRS amplitude (*B* to *E*) occurred before the actual ligation. The transient nodal rhythm noted in this tracing was observed in the two other patients with patent ductus who were studied, but the increase in the amplitude of the ventricular complex was seen in only one of the cases.

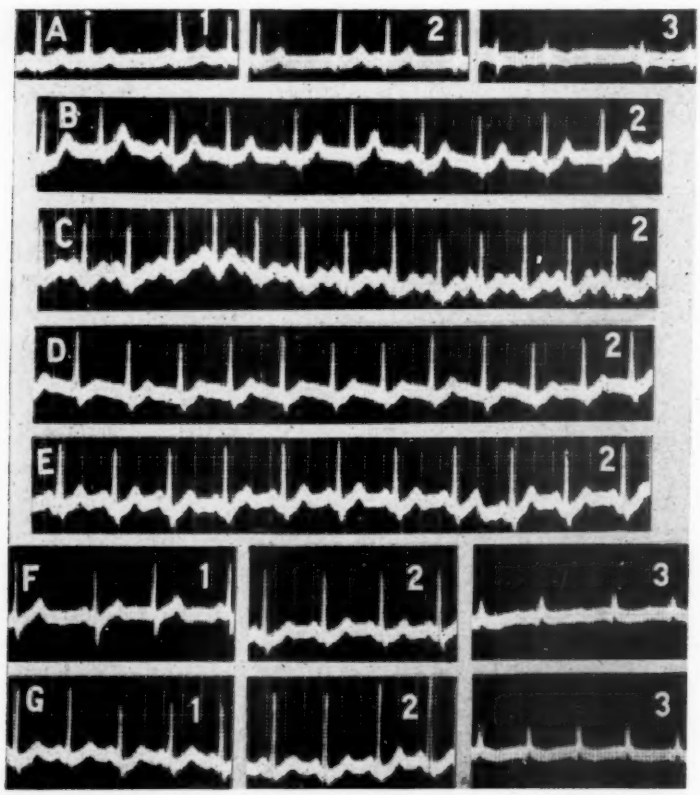

Fig. 7.—Continuous electrocardiograms taken during the ligation of a patent ductus arteriosus in a man, aged 24 years. Numbers in upper right-hand corners represent leads. Length of tracing: three hours and forty minutes. *A*, Before anesthesia; *B*, after fifteen minutes of anesthesia; *C*, thorax opened; *D*, pericardium opened; *E*, immediately before ligation of patent ductus; *F*, immediately after ligation; *G*, one hour after ligation.

It is apparent from this study that ventricular fibrillation may be the terminal rhythm when death comes gradually, for it was observed in three of eight cases. In each instance it could not be considered the actual cause of death because respirations had ceased, and, from a clinical point of view, death had already occurred. In a fourth case, ventricular fibrillation followed an intracardiac injection of adrenalin which was administered when there was no longer any evidence of cardiac activity. The sequence of events in this case (patient was a 54-year-old

man who was dying of coronary thrombosis and myocardial infarction) is seen in Fig. 8. The last spontaneous ventricular contractions (*A* and *B*) are followed by a period of asystole lasting for one minute and fifty seconds (*C*). The heart sounds were absent and there were no respirations. A needle was inserted into the heart (*D*), and a single, bizarre,

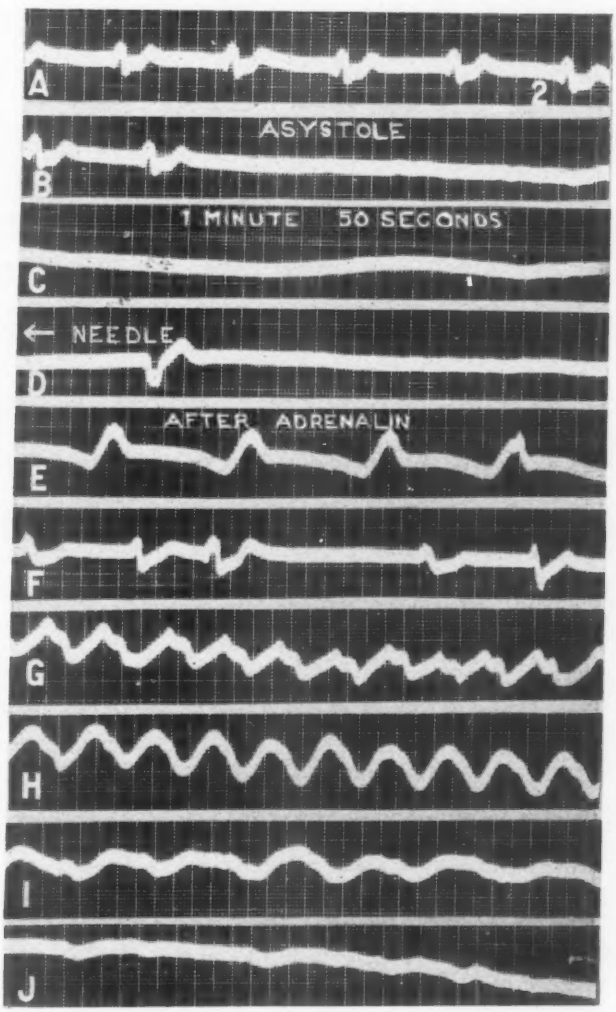

Fig. 8.—Continuous electrocardiograms (Lead II) obtained from a man, 54 years of age, dying of coronary thrombosis and myocardial infarction. Length of tracing: five hours and twenty minutes. *A*, Terminal ventricular complexes; *B*, and *C*, asystole; *D*, intracardiac needle inserted; *E*, 1 c.c. of adrenalin injected; *F*, ventricular complexes of bizarre type; *G*, *H*, and *I*, ventricular fibrillation; *J*, final asystole.

ventricular complex resulted. With the injection of adrenalin (*E*), ventricular impulses of a peculiar type (F) were initiated. Ventricular fibrillation then occurred (*G*, *H*, and *I*), followed by final asystole (*J*).

In the five patients who did not have auricular fibrillation, the sino-auricular node was the first to cease its function, but, prior to that, trantient depression and reactivation of the node were not uncommon. Fig. 9 was obtained from a 57-year-old woman who was dying of myocardial infarction. The second- and first-degree heart block (*A* and *B*), with a sinus rate of approximately 100, was followed by a sinus pause and sinus bradycardia (*C* and *D*), with a rate of only 33. This rate became more rapid again (*E*), only to slow (*F*) before all sinus activity finally ceased (*G*), fourteen minutes before death (*H*).

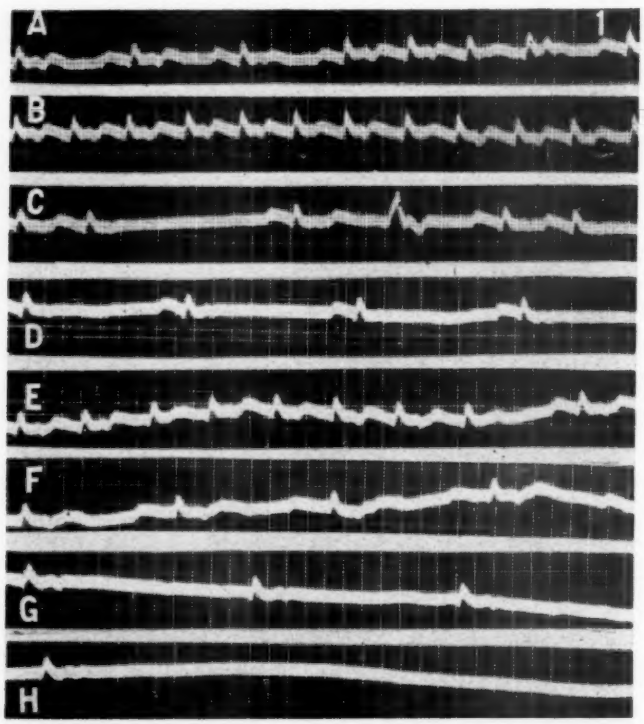

Fig. 9.—Continuous recording (Lead I) obtained from a 57-year-old woman dying of myocardial infarction. Length of tracing: three hours. *A*, Second degree heart block; *B*, first degree heart block; *C*, sinus pause and A-V block; *D*, sinus bradycardia; E, return of second degree heart block, and more rapid sinus rate; *F*, slowing of sinus rate, with 2:1 block; *G*, sinus activity ceases; *H*, death.

The occurrence of arrhythmias was not unusual among those patients who died gradually. At times the mechanisms were most difficult to recognize. Variations in rhythm are illustrated in Fig. 10, which was recorded in the last hours of a woman, aged 28 years, with mitral stenosis and congestive failure. A change from the gross irregularity of auricular fibrillation to a tendency to regular ventricular rhythm is seen in *A*, *B*, *C*, and *D*. This may have been due to either a nodal tachycardia, or to a peculiar regularization of the supraventricular impulses from the fibrillating auricles. The remainder of the tracing shows a slowing of

the ventricular rate (*E*), a change in the direction of the ventricular complexes (*F*), an intraventricular conduction defect (*G*), ventricular fibrillation (*H* and *I*), and death (*J*).

Another feature of the continuous electrocardiogram of the dying heart was a temporary inversion of the T waves, which was seen for periods of four to nine minutes in a patient with advanced constrictive pericarditis. In this instance, seven minutes before death the T waves became inverted and remained so until all cardiac activity had ceased.

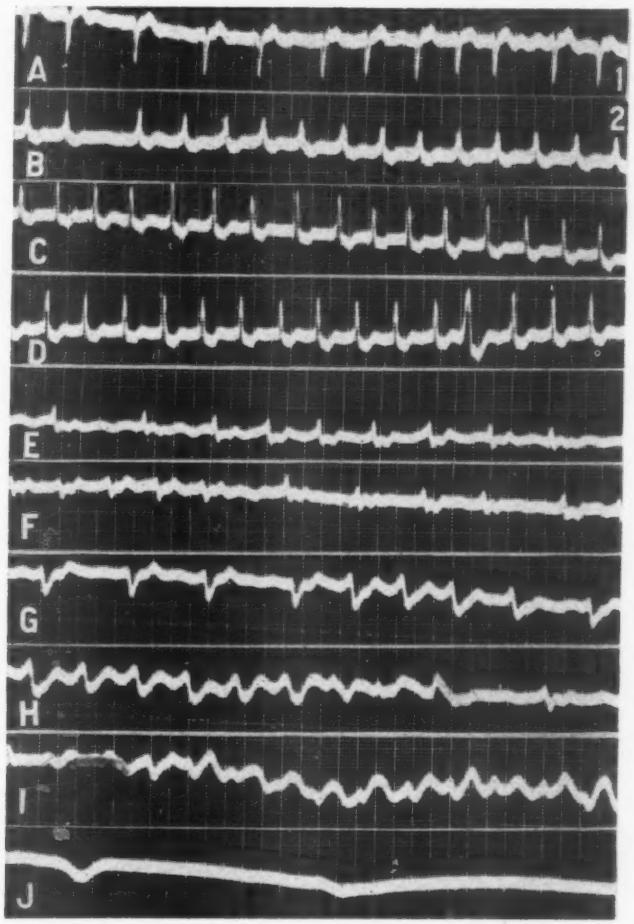

Fig. 10.—Continuous electrocardiograms taken on a 28-year-old woman dying of mitral stenosis and congestive heart failure. *A* is Lead I, and the remainder of the record is Lead II. Length of tracing: six hours. *A*, Auricular fibrillation with rapid ventricular response; *B*, *C*, and *D*, possibly nodal tachycardia; *E*, auricular fibrillation with slower ventricular response; *F*, variations in the direction of the QRS complex; *G*, intraventricular conduction defect; *H*, and *I*, ventricular fibrillation; *J*, death.

Fig. 11 is a tracing taken on a 59-year-old woman with complete heart block, right bundle branch block, and Adams-Stokes disease. Her attacks of unconsciousness lasted from several seconds to a minute. Fig. 11 *A*

represents the patient's usual electrocardiogram. In *B* and *C*, ventricular extrasystoles of different types first appear. An abnormal ventricular rhythm begins abruptly in *D* and continues through *E* and most of *F*, where it terminates quite suddenly. This arrhythmia most probably was ventricular flutter, and not ventricular fibrillation, for, although the patient was unconscious at the time, heart sounds were audible. This observation is quite significant, for such curves are often interpreted as

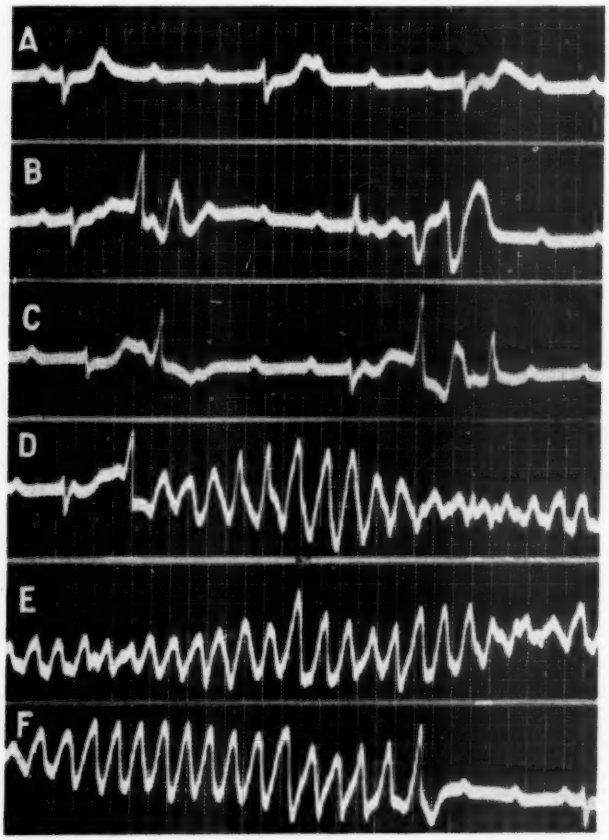

Fig. 11.—Continuous tracing (Lead I) obtained from a 59-year-old woman with complete heart block, right bundle branch block, and Adams-Stokes disease. Length of tracing: 54 minutes. *A*, Complete heart block. Right bundle branch block; *B*, and *C*, ventricular extrasystoles of different types; *D*, *E*, and *F*, ventricular flutter (heart sounds audible throughout this period); *F*, complete block.

ventricular fibrillation, a condition which is regarded as associated with failure of ventricular contraction. The fact that heart sounds were actually audible during the period of unconsciousness lends support to the concept that these bizarre, rapid undulations represent a mechanism that can well be called ventricular flutter. The above sequence of events recurred twenty-one times in a fifty-four-minute tracing, and the longest period of flutter lasted forty seconds.

A further interesting experience with complete heart block is pictured in Fig. 12. This woman was 65 years of age, and her usual apical rate was 32. Innumerable Adams-Stokes seizures were only partially controlled by the subcutaneous administration of adrenalin every four hours. Because of attacks of upper right quadrant pain, apparently due to a diseased gall bladder, she was operated upon, and, during the entire procedure, continuous electrocardiographic records were taken. Under ether anesthesia the ventricular rate increased to approximately 64 (*A*), but no further change was observed even when traction was made upon the liver and gall bladder, and when the gall bladder and common duct were artificially distended. Midway during the operation her respirations became slow and shallow, and the patient was deeply cyanotic. At the onset of this difficulty the T waves were less sharply inverted (*B*), and when her condition was most precarious they became quite shallow (*C*). Oxygen was administered and there was a prompt return of the T waves to their former configuration (*D*).

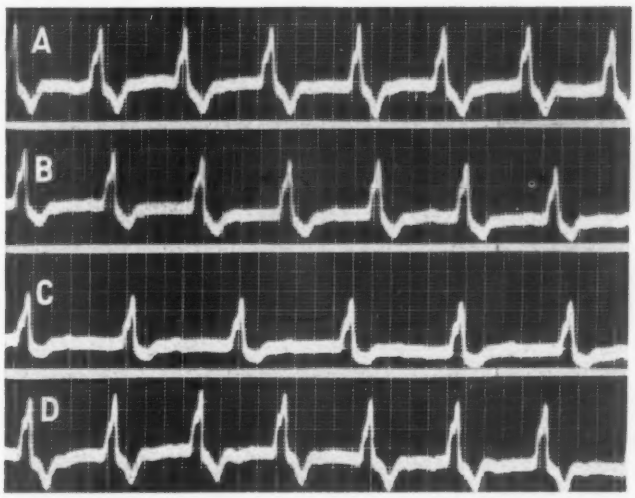

Fig. 12.—Continuous record (Lead II) on a woman 65 years of age with complete heart block, left bundle branch block, and a preoperative apical rate of 32, taken during cholecystectomy. Length of tracing: one hour and ten minutes. *A*, Ten minutes after administration of ether, and before first incision. Note sharply inverted T waves. Rate 64. *B*, and *C*, Respiratory distress. T waves become shallow. Rate 50. *D*, After oxygen. T waves again sharply inverted.

The continuous recording electrocardiograph was found to be no more difficult to operate than any ordinary portable machine. The requirements outlined under *Electrocardiographic Considerations* were fully satisfied. One tracing, heretofore not mentioned, was taken as the patient slept through the night, and no gross deviation in the recording beam was observed during the usual changes in body position. Several records were made even as the patients ate their meals. Finally, it was possible to use the apparatus in experimental work on intact large animals. Developing the film, viewing, and making enlarged reproductions

of important sections of the records were accomplished with the facilities ordinarily available in the electrocardiographic laboratory of the Peter Bent Brigham Hospital.

SUMMARY AND CONCLUSIONS

1. A continuous recording electrocardiograph was devised which is capable of taking a miniature record one-twentieth normal size upon ordinary moving picture film, and of functioning for 26.7 hours without the attention of an operator.

2. A simple enlarger was devised to view the miniature record at normal size, and to make suitable photographic reproductions.

3. The apparatus is as accurate and sturdy as the ordinary portable electrocardiograph.

4. Several interesting observations have been noted thus far. Ventricular fibrillation has been found to follow, rather than precede, death in some cases. Electrocardiographic curves generally regarded as indicative of ventricular fibrillation have been observed to occur while heart beats were audible, and therefore are better designated as ventricular flutter. Attention has also been called to other transient changes in the electrocardiogram that could be detected only by continuous tracing.

The authors wish to express their thanks to Lt. M. A. Abel, M.C., for his suggestions in connection with the continuous recording electrocardiograph.

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Clinical Report

A RARE CASE OF CONGENITAL HEART DISEASE, WITH INTERVENTRICULAR SEPTAL DEFECT, ATRETIC PULMONARY ARTERY, DEXTROPOSITION OF THE AORTA, BICUSPID RIGHT ATRIOVENTRICULAR VALVE AND SUPERIMPOSED SUBACUTE VEGETATIVE ENDOCARDITIS

MYER SOLIS-COHEN, M.D., JERRY ZASLOW, M.D., AND MEYER H. ROLNICK, M.D.
PHILADELPHIA, PA.

CASES of complete atresia of the pulmonary artery, although rare, have been reported previously.[1-4] In one case the patient lived to be 33 years of age.[1] However, we have been unable to find any cases of bicuspid right atrioventricular valve in the literature. In the case presented in this paper there were not only complete atresia of the pulmonary artery, an interventricular septal defect, and dextroposition of the aorta, but also a bicuspid atrioventricular valve on which was superimposed a subacute vegetative endocarditis. We believe this combination is unique.

CASE REPORT

L.D., an 8-year-old Italian girl, was admitted to the Pediatric Service of the Jewish Hospital in Philadelphia, Oct. 27, 1942, complaining of dyspnea, cyanosis, swelling of the abdomen, and fever of two weeks' duration.

Family History.—The family history was noncontributory. There was one sibling, who was essentially normal.

Previous Medical History.—The child was a premature baby of eight and a half months. She was cyanotic at birth, and always had had blue lips and spells of dyspnea.

When 17 months of age she was admitted to the Memorial Hospital, Philadelphia, with a diagnosis of thrush, and was discharged after nine days. No cardiac abnormalities were noted on the hospital chart at that time.

The child seemed normal, except for her cyanotic lips and occasional attacks of dyspnea, but was subject to frequent attacks of coryza and cough. Nevertheless, she was able to play almost as actively as other children of the same age.

When she was about 2½ years old, the child developed cough, fever at night, and dyspnea on walking. The cough persisted even after the fever had subsided. Her physician made a diagnosis of congenital heart disease, and sent her to the Philadelphia General Hospital, where she remained for five weeks.

From the Pediatric and Pathological Services of the Jewish Hospital, Philadelphia.
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The child had an acute upper respiratory infection when admitted. Dyspnea, cyanosis, especially of the lips, a swollen face, moderate pallor, pale and bluish sclera, and prominent pulsation of both carotid arteries were noted on admission.

The chest was asymmetrical because of a decided prominence and enlargement of the precordium. A systolic thrill was felt over the precordium. The apex beat was felt in the sixth intercostal space in the anterior axillary line. Cardiac dullness extended from the left anterior axillary line to a slight distance to the right of the sternum. The heart's action was rapid and the rhythm was normal. There were loud and overlapping heart murmurs which were difficult to separate into their components. A blowing systolic murmur was heard best in the mid-precordium. A diastolic murmur was heard at the apex. The aortic second sound was clear. The pulmonic second sound was obscured by duplication of the closing sound, plus other varied sounds heard over the precordium.

The lungs were negative except for occasional râles at both bases.

The abdomen was prominent, but soft and symmetrical. The liver was smooth, and extended 1 cm. below the umbilicus. The spleen was not palpable.

There was slight clubbing of the fingers.

The hemoglobin was 71 per cent; there were 4,650,000 erythrocytes and 14,000 leucocytes, of which 46 per cent were polymorphonuclear neutrophiles and 54 per cent were lymphocytes.

A radiologic examination, made three days after admission, showed general, marked enlargement of the heart; its anterior border was against the chest wall. Except for the aortic knob, the heart presented a large, globular outline. There was slight haziness in the lungs, due to decompensation. The main bronchi were not visualized.

A radiograph, taken six days later, disclosed no change in the size and contour of the heart. Most of the enlargement appeared to be of the right ventricle. In the anteroposterior view there was no displacement of the esophagus, but in the oblique view there was slight posterior displacement.

An electrocardiogram, taken four days after admission, showed that the T waves were upright in Lead I and the S-T segments depressed in Lead II. Right axis deviation was present, which, in the presence of a congenital heart condition, was regarded as suggestive of a right-sided lesion.

The child gained weight rather rapidly while in the hospital, and the upper respiratory infection cleared up. Her general condition, however, was not good. The child stood up and walked about her crib, but she was not active and her heart often seemed badly decompensated.

The diagnosis on admission was: Congenital heart disease, with patent interventricular septum (?); patent ductus arteriosus (pulmonary stenosis).

Three days after her discharge from the Philadelphia General Hospital the child was admitted to the Children's Hospital, Philadelphia, with a diagnosis of bronchopneumonia complicating congenital heart disease.

Three times during the following ten months she was readmitted to the Children's Hospital with upper respiratory infections complicating attacks of cardiac decompensation.

Two months after the last admission the child developed fever, anorexia, and cough, and was given a cough medicine. She seemed

to improve and lost her fever, but the cough became worse and dyspnea developed.

She was again admitted to the Children's Hospital, with a diagnosis of bronchitis and cardiac failure. At this time the heart was greatly enlarged, larger even than on her previous admissions. A loud, apical, blowing, systolic murmur was heard plainly through the chest posteriorly; it became fainter in the mitral region, where there was a definite, short, high-pitched, diastolic murmur. Both the liver and spleen were enlarged. Fluoroscopic examination at that time showed a markedly enlarged heart, ovoid in shape; the transverse diameter was the wider, and the left border approached the chest wall. No mediastinal shadow was noticed on the left, but on the right an actively pulsating vascular shadow was present above the heart, parallel to the spine. In the center of this vascular mass there seemed to be a shadow. There was no special prominence in the region of the pulmonic conus.

The electrocardiogram showed marked right axis deviation.

The patient improved with sulfonamide therapy, but this had to be discontinued because of leucopenia. Two weeks later she developed nasopharyngitis, but soon improved with sulfonamide treatment and was discharged.

The child then remained in fair health for a period of about four years, during which she had no fever or cyanosis, according to her mother.

Physical Examination.—Examination at the time of admission to the Jewish Hospital revealed an emaciated, cyanotic, and moderately dyspneic white female child, aged 8 years and 4 months, with marked clubbing of the fingers and cyanosis of the fingers and toes. The pharynx was injected and the tonsils were hypertrophied and infected. There was visible pulsation of the veins in the neck. The left border of the enlarged heart was in the midaxillary line. The heart beats were 140 a minute and regular. A loud, blowing, systolic murmur was heard over the entire chest and back, with maximal intensity in the third left intercostal space just to the left of the sternum. The blood pressure was 90/70 in the arms, and 120/80 in the legs. There were a few subcrepitant râles at the bases of the lungs. The abdomen was enlarged. The lower border of the liver was 4 cm. below the costal margin in the nipple line on the right. The spleen extended down into the pelvis. Both organs were smooth and not tender. There was no evidence of ascites or edema of the ankles. No petechiae were seen in the skin, nail beds, sclerae, or fundi of the eyes. There was moderate, generalized lymphadenopathy. The rectal temperature was 102° F. The respiratory rate was 30 per minute.

According to Dr. Alexander Margolies, the cardiologist to the hospital, the most likely diagnosis was the Eisenmenger complex (ventricular septal defect, dentroposition of the aorta, and right ventricular hypertrophy), although the tetralogy of Fallot (the above plus pulmonic stenosis) was considered.

Course in Hospital.—The patient's course in the hospital was irregular, but she grew progressively worse. The temperature ranged between 99° F. and 104° F., at times reaching 106° F. There were several frank chills. The radial pulse rate varied between 80 and 160 beats per minute. The dyspnea and cyanosis became worse, necessitating the use of an oxygen tent most of the time. The patient was given digitalis to the point of tolerance. Although the patient appeared

relatively comfortable at times, the signs of cardiac failure became more marked. Chills became more frequent. Despite constant oxygen therapy, digitalization, and sulfonamide therapy, the patient died Feb. 16, 1943.

Laboratory Studies.—Urinalyses showed an acid urine with a specific gravity varying between 1.020 and 1.030, traces of albumin, but no sugar or acetone. Microscopic examination of the urine showed a few leucocytes per high-power field, infrequent erythrocytes per high-power field, and, on numerous occasions, many hyaline and granular casts.

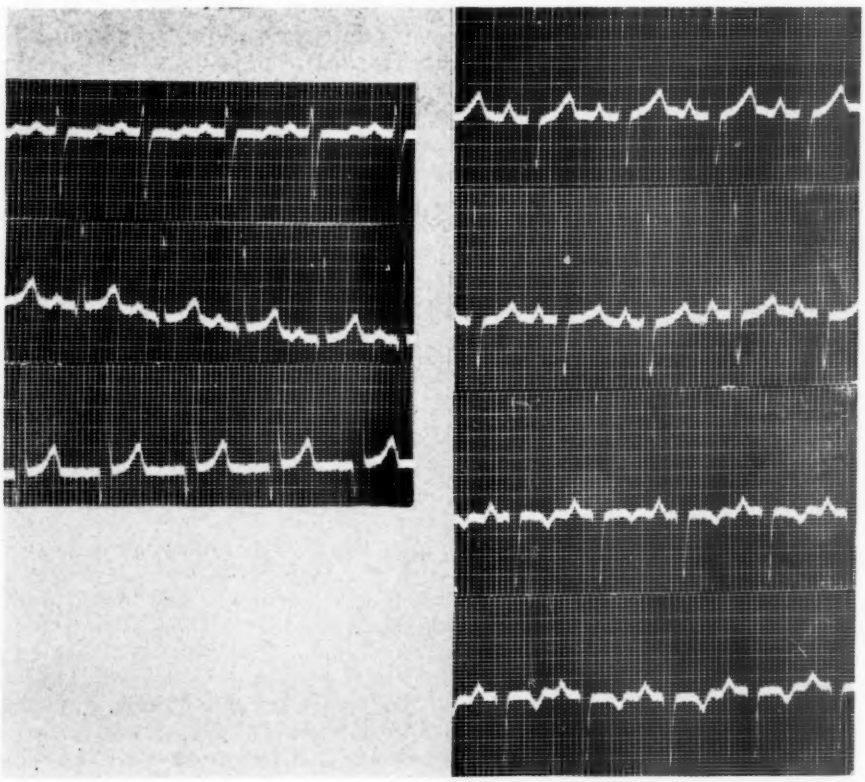

Fig. 1.

Smears and cultures of catheterized urine specimens were always negative. Although the two-hour phenolsulfonephthalein excretion test showed 25 per cent excretion in the one-hour specimen and 10 per cent excretion in the two-hour specimen, the Fishberg concentration test twice showed a concentration up to 1.030, and the blood urea on several occasions failed to exceed 15 mg. per 100 c.c. of blood. Blood examinations showed an average hemoglobin of 11.4 Gm. (83 per cent), 4,000,000 erythrocytes, and a leucocyte count which varied from 5,000 to 8,000, with a differential count of 54 per cent neutrophiles and 46 per cent lymphocytes. No abnormality of the cells was noted on smear. Blood platelet counts were normal. A bone marrow aspiration biopsy showed nothing abnormal. Of twelve blood cultures taken during peaks of fevers or chills, eleven remained sterile, and one was reported

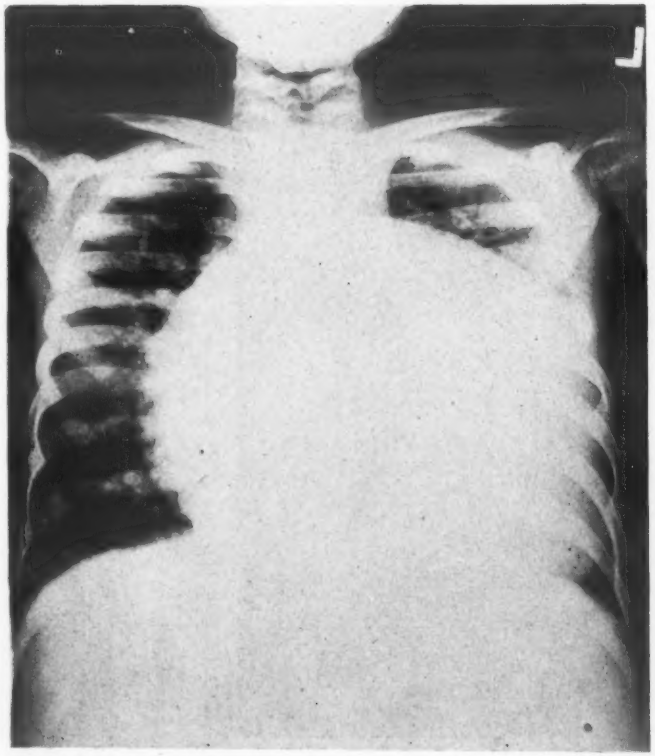

Fig. 2.

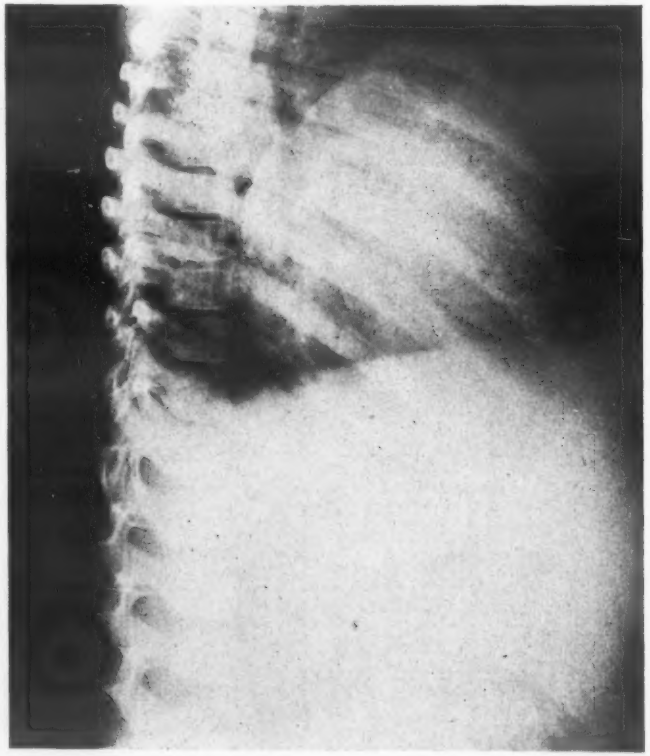

Fig. 3.

Fig. 2.—Notice diffuse, egg-shaped enlargement of entire heart. Absence of normal shadows of the great vessels. Trachea not displaced.

Fig. 3.—Lateral view. Notice encroachment anteriorly and posteriorly of the heart on the anterior and posterior mediastinal spaces. Again the egg-shaped appearance of the silhouette.

as showing a Gram-positive diplococcus, identification of which was impossible. Blood smears for malaria parasites were negative. The stools were reported as normal. Serum agglutination tests for typhoid fever, paratyphoid fever, and the Weil-Felix reaction were negative. A heterophile antibody agglutination test was positive up to a 1:8 dilution. All blood chemical examinations were negative. The blood Wassermann reaction was negative.

An electrocardiogram revealed evidence of right axis deviation (Fig. 1). An orthodiagram disclosed an enormously enlarged heart (103 per cent above the predicted normal), a cardiothoracic ratio of 73 per cent, and a globular configuration. No prominence or pulsations were noted in the pulmonic area. Radiologic examination of the chest showed a normal diaphragm, tremendous enlargement of the heart to the left,

Fig. 4.—Abdomen, showing gross enlargement of the liver and spleen.

some enlargement to the right, and considerable enlargement both anteriorly and posteriorly, and intensification of the vascular markings in the pulmonary fields. (Figs. 2 and 3.)

A radiograph of the abdomen revealed an enlarged liver and spleen. (Fig. 4.) Roentgenograms of the long bones failed to show any evidence of lipoid storage disease, leucemia, or renal rickets.

POST-MORTEM OBSERVATIONS

The autopsy was performed by one of us (J. Z.) two hours after death. The skin was intensely cyanotic. The veins of the neck were

engorged. The abdomen was distended. The fingers were clubbed and cyanotic. There were no petechiae.

Heart.—The organ weighed 290 Gm. The muscular tone was good. The color was beefy-red. The left ventricular wall measured 10 mm. in thickness. The right ventricular wall measured 8 mm. in thickness. Both ventricular cavities were markedly dilated, especially the right. The auricular appendages contained no thrombi. The atria appeared normal. The mitral valve was normal in thickness and appearance. The right atrioventricular valve had only two cusps, a large posterior one and a smaller anterior one. On the anterior cusp there were a few vegetations covering an area of 4 mm. on the atrial surface. The vegetations were polypoid (Fig. 5). There was an interventricular septal defect in the upper anterior portion of the septum, measuring 3 cm. in diameter. The aorta communicated with both ventricular cavities and was markedly dilated. There was no pulmonary artery, or any vestige of such a structure (Fig. 6). The foramen ovale was closed. The branches of the descending thoracic aorta were markedly enlarged.

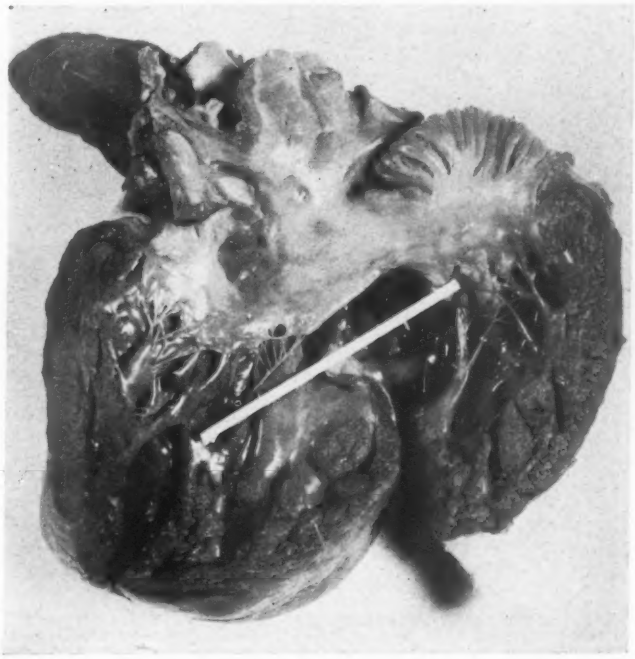

Fig. 5.—This view shows the bicuspid right atrioventricular valve. On the left is the large posterior cusp. The indicator points to the polypoid vegetations on the smaller anterior cusp.

Lungs.—The tracheobronchial tree was congested. No pulmonary artery was seen entering the hilum of the lung. The pulmonary veins, however, were traced back to the left atrium. There were numerous areas of atelectasis. No areas of infarction were seen.

Spleen.—The organ weighed 650 grams. The capsule was smooth. The organ cut with uniform and increased resistance. On cut section, the pulp was intensely congested, and the follicles were distinctly prominent and enlarged.

Kidneys.—Each weighed 160 grams. The capsules were smooth and stripped easily, leaving smooth congested surfaces. On cut section the parenchyma was intensely congested. The relationship of medulla to cortex was normal. The pelves and ureters were normal. No areas of infarction were seen.

Liver.—Weight, 1,500 grams. The surface was smooth. The organ cut with uniform resistance. On cut section there was a "nutmeg" appearance. The intervening parenchyma was pale and softer than normal.

All the other organs appeared grossly normal.

A *blood culture* taken at the time of autopsy remained sterile. A *smear and culture of the vegetation* on the heart valve failed to reveal any organisms. No anaerobic culture technique was used for any of the cultures taken during life or at autopsy.

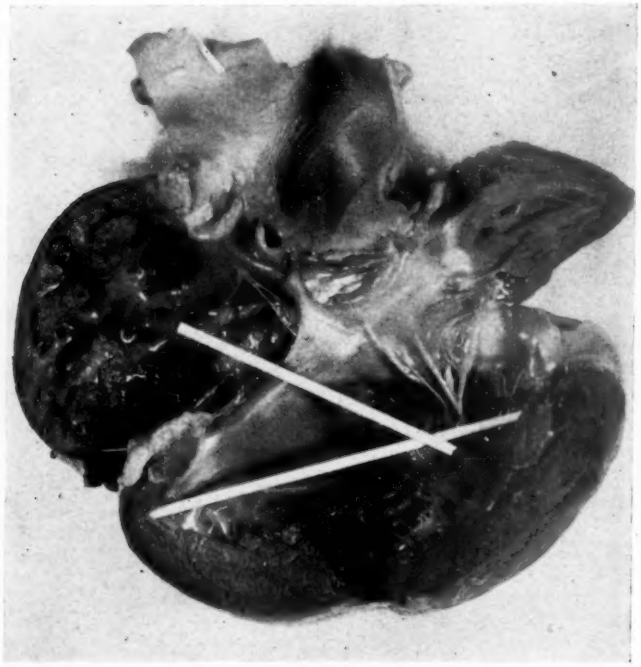

Fig. 6.—View of the heart from above and anteriorly. The upper indicator is passing through the interventricular septal defect. The right ventricular cavity is on the left. Note the large aorta overriding both ventricular cavities. Note the absence of a pulmonary artery. The aorta is markedly enlarged.

Microscopic examination of the organs revealed the following facts:

Heart: Hypertrophy and cloudy swelling. Sections of the vegetation on the valve revealed deeply set colonies of organisms. There was a fibroblastic reaction beneath the vegetation. The organisms were gram-positive.

Lungs: Chronic passive congestion; chronic interstitial pneumonitis.

Spleen: Chronic passive congestion; reticulo-endothelial hyperplasia; marked hemosiderosis.

Kidneys: Focal glomerulonephritis; marked toxic nephrosis.

Adrenals: Hyperplasia of the medulla.
Liver: Chronic passive congestion; hepatosis; focal necrosis.
Pancreas: Chronic passive congestion.

COMMENT

The mechanics of the circulation when the pulmonary artery is atretic has been explained in previous reports as due to a compensatory enlargement of the bronchial arteries; these vessels take over the functions of the absent pulmonary vessels. It would appear, then, that the larger the bronchial arteries become, the better is the prognosis. This has been shown to be true of two patients who lived for long periods of time, and in whom the bronchial arteries were the size of pulmonary vessels.

It is not uncommon for subacute bacterial endocarditis to involve congenitally defective valves. Gelfman and Levine[5] found over 60 cases of bacterial endocarditis in 634 cases of congenital heart disease. In their review of the literature, as many as 30 per cent of congenitally defective hearts were found to be also affected by endocarditis. The reason for this is unknown, and it is not our purpose to seek an explanation here. Although there was only one positive blood culture, and it was impossible to identify or isolate the organism, the clinical course suggested subacute bacterial endocarditis. This was corroborated at autopsy, when the vegetations characteristic of the disease were found on the bicuspid right atrioventricular valve. In interventricular septal defects the endocarditis is more often found on the margins of the defect, and in one case was found on the right ventricular wall opposite the malformation.[6] The interventricular septal malformation was spared; the valve was affected.

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Abstracts and Reviews

Selected Abstracts

Green, H. D., Cosby, R. S., and Radzow, K. H.: Dynamics of Collateral Circulations. Am. J. Physiol. 140: 726, 1944.

A *cognate* system is defined as a vascular bed, the blood flow characteristics and primary artery and vein of which are being studied. It includes only those arterioles, capillaries, and veins which received blood from the cognate artery when the latter is receiving blood from the aorta or from a reservoir at a pressure equal to aortic mean pressure while all collateral arteries are being supplied from the aorta. Collateral systems include all arteries, capillaries, and veins which communicate with the cognate system by pre- and/or post-capillary anastomotic channels.

The magnitude of the exchange of blood across these anastomotic channels under various conditions was studied by measuring the flow of blood from a reservoir into the cognate artery at each of a series of pressures from 0 to above mean aortic pressure (a) while the collateral arteries were receiving blood from the aorta, and (b) while the collateral arteries were also being perfused from the reservoir at the same pressure as the collateral artery.

In experiments on the hind extremity of the dog, in which the collateral arteries were receiving blood from the aorta, and in which the resistance to flow in the arterial anastomotic channels was small in relation to that in the cognate capillary bed, it was observed that: (a) flow into the cognate artery at a perfusion pressure of 15 mm. Hg greater or less than the aortic mean pressure, differed from the flow through the cognate bed by 40 to 300 per cent; and (b) although the flow through the cognate bed was unchanged, the flow into the cognate artery under a constant head of pressure provided by a reservoir, increased 40 to 1900 per cent as a result of fall in the pressure in the collateral arteries such as might be produced by a decline of aortic pressure.

The effective collateral flow is defined as the rate at which blood will flow from the collateral beds through the anastomotic channels and thence through the cognate bed immediately after occlusion of the cognate artery. Measurement of the backflow from the distal end of the cognate artery provides a rough measure of the effective collateral flow. A better estimate of the effective collateral flow, with respect to the normal flow through the cognate bed at mean aortic pressure, is given by the ratio of the peripheral arterial pressure in the cognate artery, minus 20, to the mean aortic pressure. A still more accurate measure of the effective collateral flow is obtained by recording the flow into the cognate artery while perfusing the cognate and collateral arteries at a pressure equal to the peripheral arterial pressure (above), and comparing this with the flow through the cognate bed at mean aortic pressure. In various portions of the hind extremity of the dog, the effective collateral flow varied from 9 to 85 per cent of normal flow through the cognate bed.

Studies of the relationship of perfusion pressure to flow through the cognate bed may be satisfactorily accomplished in most vascular regions by perfusing the collateral arteries at the same pressure as the cognate artery. However, technical errors are very likely to occur whenever the flow into the collateral arteries is extremely large, or the anastomotic communications are very prominent.

In the presence of prominent venous anastomotic channels, outflow from the cognate vein may vary from 25 to 200 per cent of the flow through the cognate bed.

In flow studies in the distal part of extremities, the exchange of blood across both venous and arterial anastomotic channels may be effectively prevented by application of wire ligatures which tightly compress all structures except the cognate artery and vein and the nerves.

AUTHORS.

Shipley, R. E., and Gregg, D. E.: The Effect of External Constriction of a Blood Vessel on Blood Flow. Am. J. Physiol. **141:** 289, 1944.

The effect of an external constriction of a blood vessel in limiting blood flow has been considered with respect to the relationships of (1) vessel bore to volume flow, and (2) change in external to change in internal dimensions of the vessel. Experiments with an artificial system and in animals have led to the conclusions that:

The effect of a localized reduction in lumen area is primarily that of increasing the fluid friction (viscosity effect) at the site of the constriction, which results in an added "peripheral resistance" to the flow of blood and the rate of flow is thereby reduced.

The extent of flow reduction will vary in direct relation to the axial length of the constricted area, the velocity of flow, and the viscosity of the blood, and in inverse relation to the peripheral resistance of the bed and the lumen area of the vessel constriction. Since, with an intact blood vessel, it is impossible to determine all, or even most, of the above factors, an estimation of the flow reduction caused by a given constriction will be only as accurate as the estimated values placed upon the determining factors. Without the observer's knowledge, marked changes in the determining factors may occur, thereby making it impossible to predict within rather wide limits either the immediate or subsequent effects of a known constriction.

The findings presented here reveal no justification for the contention that a rather marked degree of external constriction is required to produce a significant reduction in flow through a vessel.

In comparison with other external constricting devices, the thermostromuhr cannot be regarded as having any less variable or unpredictable effect in limiting the rate of flow through the vessel to which it is applied.

AUTHORS.

Koletsky, S., and Barnebee, J. H.: "Cardiac" or Congestive Cirrhosis. Pathologic and Clinical Aspects. Am. J. M. Sc. **207:** 421, 1944.

Livers, the seat of prolonged and advanced passive hyperemia due to heart failure, sometimes show diffuse fibrosis and alteration of architectural pattern. These may properly be designated congestive cirrhosis. However, the degree of fibrosis and distortion of architectural pattern are considerably less than in well-developed Laennec's cirrhosis.

The main etiological factor is prolonged and severe hepatic venous stasis. Repeated episodes of decompensation favor the development of the lesion.

The most severe degree of fibrosis and architectural change occurred in patients with chronic constrictive pericarditis. The continual venous stasis in such cases suggests that the cirrhosis develops as a progressive process.

Congestive cirrhosis is relatively common in patients with rheumatic heart disease, both in those with mitral stenosis, and those with combined valvular lesions. It is less frequent in hypertensive patients and is uncommon or rare in other etiological forms of heart disease.

The clinical aspects of congestive cirrhosis do not provide adequate data for ante-mortem diagnosis.

AUTHORS.

Mayer, C. P., Lepera, L., and Pataro, F. A.: Character of the Precordial Ventricular Complex in ECG Tracings With Deviation of the Electric Axis to the Right. Rev. argent. de cardiol. **10**: 245, 1943.

Right axis deviation and right ventricular strain have no characteristic precordial lead pattern. A deep S wave in all positions is often found in both cases and, in the latter, a negativity of T in CF_1.

AUTHORS.

Ash, R., Rubin, M. I., and Rapoport, M.: Electrocardiographic Variations in Acute Glomerulonephritis. Am. J. Dis. Child. **67**: 106, 1944.

An analysis of the variations in serial electrocardiograms obtained from fifty children ill with a first attack of acute glomerulonephritis disclosed abnormalities in 72 per cent of the group. Abnormal variations were present in the tracings of 86 per cent of the children with clinical signs of heart failure, and in 57 per cent of those with negative or questionable cardiac findings. The incidence of clinically recognizable heart disease and of electrocardiographic variations was greater among patients in whom the blood pressure was high. At all levels of blood pressure, abnormalities in the electrocardiogram were noted more frequently than clinical evidences of cardiac involvement.

The most striking changes were observed in the T wave, consisting chiefly of flattening and inversion in one or more leads, although a transient increased amplitude of the T wave was also occasionally observed. Inversion of the T wave occurred late in the cycle and was not infrequently preceded, especially in Leads I and II, by a slightly depressed, upward bowed ST segment. Transient inversion of the T wave occurred as frequently in Lead III as in Lead I. The incidence of heart failure, however, was greater in association with inversion of the T wave in Lead I than in association with inversion of this wave in Lead III. In some instances isolated transient inversion of the T wave in Lead III may have been related to elevation of the diaphragm and change in position of the heart.

AUTHORS.

Campbell, A. M. G., Gibson, P. C., and Lane, C. R. T.: Auricular Fibrillation Late in the Course of Diphtheria. Brit. Heart J. **5**: 183, 1943.

The authors recorded the occurrence of auricular fibrillation in a man, 39 years old, which arose during his convalescence from diphtheria. It lasted for 112 days, when it was stopped by quinidine. Except for his palpitation, it was unaccompanied by any symptoms referable to the cardiovascular system. It was associated with multiple peripheral neuritis, which preceded its onset by thirty-two days. There was a family history of arteriosclerosis, and some slight evidence of this in the patient himself.

AUTHORS.

Parsons, C. G.: Complete Auriculo-Ventricular Dissociation With High Ventricular Rate in Paroxysmal Tachycardia. Brit. Heart J. **5**: 187, 1943.

A case of paroxysmal auricular tachycardia is described, in which there developed a spontaneous attack of A-V dissociation, with high auricular and ventricular rates amounting to a double tachycardia. The condition could be partly reproduced during attacks of auricular tachycardia by atropine, adrenalin, and carotid sinus pressure. The patient's heart was otherwise normal, and no drugs had been given. It is suggested that the condition is due to a form of heart block, the mechanism of which is allied to, but not identical with, the Wenckebach phenomenon.

AUTHOR.

Evans, W.: Triple Heart Rhythm. Brit. Heart J. **5**: 205, 1943.

Triple rhythm is the cadence produced by the recurrence, in successive cardiac cycles, of three separate sounds. The chief purpose of this work has been to classify triple rhythm in accord with findings on clinical, radiological, cardiographic, and, sometimes, pathologic examination of the heart, in patients presenting this auscultatory sign. The investigation has shown the need for discarding the terminology hitherto in use for triple rhythm, and adopting one that is based on the clinical condition and avoids any preoccupation with the mechanisms of the extra sound. As soon as it becomes the custom to listen specifically for a sound in addition to the more familiar first and second heart sounds, triple rhythm will be found to be common, perhaps as common as dual rhythm in patients sent for examination of the heart.

When the position of the adventitious sound in the cardiac cycle was considered along with the clinical state of the patient in 270 cases with triple rhythm, it was possible to place them in three groups. As a rule, even under the handicap of fairly severe tachycardia, the position of the extra sound could be told by auscultation, aided by the clinical data, before phonocardiography was used for scientific support.

In the first group, consisting of 205 cases and comprising 125 healthy subjects and 80 patients with right ventricular heart failure, the added sound was the third heart sound occurring in early cardiac diastole. A simple triple rhythm is distinguished from that due to right heart failure by regarding the site of maximum audibility of the sound, the effect of posture upon the sound, and the health or disease of the heart. In the second group, the fourth heart sound is added during auricular systole and at the end of ventricular systole. There were sixty patients with this variety of triple rhythm. In fourteen of them, it was the outcome of delayed A-V conduction. In forty-six patients the extra sound appeared during left ventricular failure where auricular action, although probably not the direct cause of the sound, is essential for its production because it disappears with the onset of auricular fibrillation. In the third, and least important group, an extra sound is added in late systole.

Triple rhythm is a common auscultatory sign, and it can be of great aid in the diagnosis of cardiovascular disorder. It should be sought specifically in every case, and when found, the position of the supernumerary sound in the cardiac cycle should be traced, and its significance determined in the light of clinical findings and in accordance with some classification such as that here proposed.

AUTHOR.

Marshall, R.: Persistent Truncus Arteriosus. Brit. Heart J. **5**: 194, 1943.

A persistent truncus arteriosus was found, after death, in a boy, aged 13 years, who had always been cyanosed and breathless, and had suffered from hematemesis due to esophageal varices. The cardiac murmurs had been transient; there was no endocarditis, and death was attributed to congestive failure. Electrocardiogram, radiogram, and post-mortem findings are recorded.

AUTHOR.

Goodof, I. I., and MacBryde, C. M.: Heart Failure in Addison's Disease With Myocardial Changes of Potassium Deficiency. J. Clin. Endocrinol. **4**: 30, 1944.

A case of primary atrophy of the adrenal cortices, in which death was caused by cardiac failure, is reported. Foci of necrosis of cardiac muscle were present in the walls of all four chambers of the heart. Similar foci have been described in animals which have been given large doses of desoxycorticosterone acetate, or

which have been fed a diet deficient in potassium. It is believed that such changes may play a part in producing the cardiac abnormalities occasionally seen in patients receiving replacement therapy in Addison's disease.

AUTHORS.

Thomson, H. W., and Feil, H.: Infarction of the Lateral Wall of the Left Ventricle. Pathologic and Electrocardiographic Study. Am. J. M. Sc. 207: 588, 1944.

Nineteen cases of left lateral infarction were found in 106 cases of myocardial infarcts, examined pathologically. Of these lateral infarcts, nine were recent. In these recent cases, the electrocardiograms of four (44.4 per cent) showed the pattern described by Wood, Wolferth, and Bellet.

Auricular fibrillation, or flutter, was found in five of these recent cases (55.55 per cent). This incidence may have been greater, actually, because all of the electrocardiograms showed auricular fibrillation or flutter to be temporary.

In the five recent cases without electrocardiograms diagnostic of lateral infarction, the changes were diagnostic of posterior and basal infarction in three instances. The other two cases showed auricular fibrillation, and in one of these the electrocardiogram showed slight but not diagnostic depression of the S-T segment in Lead IVR.

Two cases associated with infarction of the posterior and basal region of the left ventricle presented electrocardiograms dominated by the T_3 pattern. One case associated with anterior and apical infarction had left bundle branch block.

Seven cases of remote lateral infarction showed no characteristic pattern.

AUTHORS.

Raab, W., and Soule, A. B., Jr.: Rationale and Results of Roentgen Treatment of the Adrenal Glands in Angina Pectoris. Am. J. Roentgenol. 51: 364, 1944.

Angina pectoris on effort, emotion, and so forth, is believed to be due, essentially, to the well-known, acutely anoxiating effect of adrenaline discharges from the adrenal glands upon the heart muscle, the sclerotic coronary arteries of which are unable to dilate adequately and thus to overcome the resulting myocardial anoxia. Clinical and experimental evidence is presented for this theory.

The state of abnormal irritability of the adrenal secretory mechanism which was found to be a characteristic of angina patients could be abolished through roentgen irradiation of the adrenal region without ensuing damage to the basic, normal function of the glands. This was demonstrated objectively by quantitative chemical hormone determinations in the blood before and after treatment, and by the normalization of pathologic electrocardiograms.

Of forty-two typical angina patients treated in Burlington, Vermont, with irradiation of the adrenal region, 74 per cent were either completely freed of their anginal complaints or, at least, improved for periods ranging between five and forty-five months with an average of two years up to the present.

Nine of the eleven unimproved patients had not received three series of roentgen treatments, and thus cannot be considered as definite failures.

No untoward side effects were noted except short episodes of nausea in a few cases.

Death occurred in seven out of the forty-two patients treated during the past four and one-half years.

AUTHORS.

Cassels, D., and Steiner, P.: Mycotic Endocarditis: Report of a Case With Necropsy; Review of the Literature. Am. J. Dis. Child. 67: 128, 1944.

Studies of a sufficient number of cases of mycotic endocarditis are available to indicate that this condition represents a subdivision of the general category of subacute bacterial endocarditis. Frequently, as in bacterial endocarditis, valvular lesions from other infections are present previous to the onset of the endocardial infection. The clinical course appears to be indistinguishable from that of subacute bacterial endocarditis, and the laboratory findings, with the exception of blood cultures, are similar. In cases where the clinical findings suggest the diagnosis of subacute bacterial endocarditis, it is obvious that unusual organisms present in blood cultures should not be casually dismissed as contaminants, especially if these are present in repeated cultures. Likewise, negative blood cultures suggest the use of special mediums and especially long periods of incubation.

As interest in mycotic infection in man increases, it seems likely that mycotic endocarditis will be found to be more common than a survey of the literature indicates and that the variety of organisms responsible for the infection will be found to be diverse.

The case reported by the authors raises the question whether adequate treatment with sulfonamide compounds may not be of value in treatment in some instances of mycotic infection.

AUTHORS.

Feldt, R. H.: Sulfanilamide as a Prophylatic Measure in Recurrent Rheumatic Infection. A Controlled Study Involving 131 "Patient-Seasons." Am. J. M. Sc. 207: 483, 1944.

Sulfanilamide in small, daily doses was given to rheumatic children in the Cardiac Clinic of the Milwaukee Children's Hospital during the autumn, winter, and spring of 1941-1942 and 1942-1943. Altogether, eighty-nine patient-seasons were represented in the treated group and forty-two patient-seasons in the control series. No rheumatic recurrences appeared among the children who took sulfanilamide. There were three (7.2 per cent) major and minor recurrences among control patients. Questionable rheumatic episodes were observed with greater frequency in the control group. The incidence of positive beta hemolytic streptococcus throat cultures was approximately the same in the two groups. Manifestations of sulfanilamide toxicity were neither frequent nor severe. Sulfanilamide is recommended as a relatively safe and effective prophylactic measure against recurrent rheumatic infection.

AUTHORS.

Shank, R. E., Coburn, A. F., Moore, L. V., and Hoagland, C. F.: The Level of Vitamin A and Carotene in the Plasma of Rheumatic Subjects. J. Clin. Investigation 23: 289, 1944.

The level of vitamin A and carotene in the plasma is related to the intake of vitamin A in the diet of rheumatic subjects.

Irrespective of the concentration prior to the onset of disease activity, there is a fall in the level of vitamin A in the plasma with the development of acute rheumatic fever. The concentration of carotene in the plasma is not significantly changed during rheumatic attacks.

The degree of decrease of vitamin A in plasma varies directly with the intensity of the rheumatic attack. In severe attacks, concentrations in the plasma varied between 0 and 70 I.U. of vitamin A per 100 c.c. plasma.

Patients with rheumatic fever show delayed or decreased absorption of vitamin A, or metabolize it in an abnormal manner.

AUTHORS.

Auerbach, O., and Stemmerman, M. G.: The Development of Pulmonary Tuberculosis in Congenital Heart Disease. Am. J. M. Sc. 207: 219, 1944.

A study has been made of thirteen patients who had congenital heart disease and contracted pulmonary tuberculosis. Upon seven of these patients post-mortem examinations were performed. The most common congenital defect was pulmonary stenosis, which was present in all cases which came to autopsy, implying a certain predisposition of these patients to tuberculosis.

A composite picture of the typical case, including clinical, physiologic and pathologic studies, has been presented. From this material it may be concluded that the pulmonary tuberculosis runs a course typical of that disease, irrespective of the cardiac lesion. The functioning of the defective cardiac system is affected very little by the superimposed respiratory infection.

In view of this observation, together with the fact that these patients succumbed to pulmonary involvement rather than failure of the defective cardiovascular system, active treatment of tuberculosis is recommended. Pneumothorax induced in 5 of the patients did not lead to congestive heart failure in any instance. The importance of other surgical forms of collapse therapy for these patients has been discussed.

AUTHORS.

Howell, T. H.: Heart Failure in the Aged. Brit. Heart J. 6: 20, 1944.

The causes and forms of heart failure in seventy-five old persons are described.

The commonest causes of failure were high blood pressure, disease of the coronary artery, and myocardial toxemia.

In 13 per cent of the cases, the cause of heart failure remained uncertain after repeated clinical examination.

The occurrence of "forward" heart failure, with peripheral ischemia is described, and the importance of arteriosclerosis in producing circulatory failures is stressed.

AUTHOR.

Sensenbach, W.: Effects of Unilateral Nephrectomy in Treatment of Hypertension: An Evaluation. Arch. Int. Med. 73: 123, 1944.

Only five of the seventy-five cases of hypertension taken from the literature meet the requirements for cure after nephrectomy. Approximately one-third of the patients had a fall in blood pressure in normal levels, but had been followed for less than two years at the time their cases were reported. One-third had a reduction in blood pressure, but remained hypertensive, while in one-third the blood pressure was unchanged or increased in severity.

The most common pathologic condition in the removed kidneys was chronic pyelonephritis.

A two year follow-up period is necessary before hypertension can be considered cured by nephrectomy.

Cases in which unilateral nephrectomy is indicated for hypertension are rare, and there is need for more careful selection of such cases.

The removal of a kidney, if it retains any function at all, is likely to increase the severity of the hypertension, rather than to improve it. This is true even though the function of the opposite kidney is entirely normal.

The usual tests of renal function may at times be unreliable, and in the light of this fact, special care and consideration must be given to evaluation of the function of each kidney before nephrectomy is performed.

The age of the patient and the duration of the hypertension are additional factors of importance in the selection of suitable cases for nephrectomy in the treatment of hypertension.

AUTHOR.

May, J.: The Frei Reaction in Arteriopathies of the Lower Extremities. Rev. argent. de cardiol. **10**: 257, 1943.

The Frei reaction, which is considered by the author as specific for poradenitis, was tested in patients with arterial diseases of the lower limbs. It is recommended to use 0.1 to 0.3 c.c. of a good antigen, so that cases with slight allergy do not escape detection.

Twenty-two patients were studied: two with a history of syphilis were Frei positive. Of the other twenty, without syphilitic antecedents, eleven had Buerger's disease and, of these, seven were Frei positive; and nine had arteriosclerosis obliterans. Two of these were senile and Frei negative; the other seven (ages between 39 and 60 years) were Frei positive.

Treated with sulphamides (2 grains per day) and emetic tartrate (0.02 grains on alternate days) complete reintegration was obtained in the two syphilitic patients. In the thromboangiitis obliterans cases two were cured, a few were improved, and the treatment failed in others. In four cases of arteriosclerosis obliterans a slight improvement was obtained.

AUTHOR.

Sheehan, J. F.: Foam Cell Plaques in the Intima of Irradiated Small Arteries. Arch. Path. **37**: 297, 1944.

An uncommon, or, at least, rarely described, lesion of small arteries (100 to 500 microns in external diameter) has been observed in several irradiated organs. The lesion consists of a plaquelike thickening of the intima, due to a collection of foam cells alone or of foam cells mixed with various other cells, fluid, fibrin, or hyaline material, between the endothelium and the internal elastic membrane. Pathologic changes may be found in the adjacent internal elastic membrane, media, and adventitia, but these structures are often normal. The plaque may cause marked narrowing, or even occlusion, of the lumen of the vessel. Thrombosis, fibroblastic proliferation of the intima, or deposition of elastic tissue in the thickened intima seldom result.

These foam cell plaques have been found in the arteries of organs subjected to roentgen therapy only, radium therapy only, or to both combined.

The plaques probably result from migration into the intima from the blood stream of lymphocytes and monocytes and subsequent transformation of these into foam cells by their ingestion of lipids which have been freed by the dissolution of red cells in the intima, or which have accumulated in the intima after passage across portions of the endothelium rendered more permeable than normal by irradiation.

The foam cell plaques in irradiated small arteries closely resemble the early lesion of atherosclerosis.

AUTHOR.

Dalton, J. W., and Nuzum, F. R.: The Effect of Sodium Thiocyanate on the Pressor Action of a Renin-Like Substance. Am. J. Physiol. **141**: 415, 1944.

By subcutaneous injection or by mouth, sodium thiocyanate will minimize the pressor effect of unit amounts of a renin-like substance when injected intraperitoneally into normal and sensitized rats.

There is some indication that sodium thiocyanate does not act directly to perform this function but that it may activate some other mechanism in the body which is not so easily dissipated as sodium thiocyanate and which will continue to eliminate the pressor effect.

AUTHORS.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

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